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Jonathan L. Benumof, MD, *Consulting Editor*

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ANESTHESIA AND NEW SURGICAL
PROCEDURES

A. Scott Wheeler, MD, *Guest Editor*

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Preface

During the past several decades, advancements in medicine have blossomed rapidly. These developments, both pharmacologic and technical, have involved all medical specialties. In anesthesiology, physicians and nurses have had to familiarize themselves with many new pharmaceuticals, instruments for administration of anesthesia, and patient monitoring devices. Additionally, they have had to provide services for new diagnostic and surgical modalities, which require analgesia, anesthesia, or a quiescent individual. To ensure a safe and optimal perioperative environment, members of the anesthesia team must be cognizant of the more important pathophysiologic, surgical, and anesthetic considerations involved in each of these new processes.

This issue of *Anesthesiology Clinics of North America* addresses the management of 12 newer methods, necessitating our involvement. Together, Dr. Jonathan Benumof, the editorial consultant, and I selected topics that we believed to be either controversial, increasingly utilized clinically, or accompanied by unique anesthetic requirements. The reader will notice that several of these procedures are not really new but rather are becoming employed in many communities as well as university hospitals (for example, kidney transplantation, replantation of extremities, and anterior spinal column surgery). Thus, although the surgical method may not be new, the requirements for anesthesia may be new to the experienced clinician practicing in a center, which heretofore had not provided the procedure. In contrast, other articles discuss the management of truly new surgical techniques—pancreatic transplantation, adrenal caudate transplants, and in vitro fertilization—which may be controversial because of limited outcome studies but nevertheless necessitate the anesthesiologist's awareness. Finally, several articles involve the clinical application of recent biomedical technologies (laser therapy, arthroscopy of temporomandibular joints, and magnetic resonance imaging), which often warrant special safety precautions for both the patient and anesthetist. During the care of the person undergoing laser therapy to the airway

or magnetic resonance imaging, the anesthesiologist and nurse anesthetist may have to divert themselves away from traditional modes of surgical anesthesia, sometimes providing services in remote locations. This requires forethought, sound judgment, and effective communication with primary care individuals.

This guest editor sincerely hopes that you, the reader, find this volume to be timely, informative, and pertinent to your clinical practice. I am indebted to Jon Benumof, MD, for giving me this opportunity, to Margaret Burns of W. B. Saunders for her support and assistance, and to Cheryl Owens for her secretarial and organizational skills. Most importantly, the authors have engendered much gratefulness and respect for having taken time out of their busy schedules to prepare such nicely written manuscripts.

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Foreword

Advances in medical technology are progressing at a geometric rate and many recently introduced techniques have already become accepted clinical procedures. Anesthesiologists must comprehend all the technical, surgical, and medical nuances involved in the clinical application of these new methods in order to provide optimal, safe, and rational anesthetic care. This issue of *Anesthesiology Clinics of North America* addresses these considerations for 12 newer anesthesiologically challenging procedures.

Some articles discuss procedures that represent the clinical application of truly new techniques: namely, pancreatic transplantation, laser therapy of the airways, caudate to adrenal transplants, in vitro fertilization, and nuclear magnetic resonance imaging. In some of these methods, for example, laser therapy and nuclear magnetic resonance imaging, the anesthesiologist will find that these are significant constraints to traditional anesthetic management that are imposed by the therapeutic or diagnostic devices themselves.

Other articles discuss management of procedures that will seem new to many experienced anesthesiologists because of the rapidity with which they are gaining increased usage in university and community hospitals. These techniques are renal and liver transplantation, anterior spinal column and spinal cord surgery with use of double-lumen endotracheal tubes and evoked potential monitoring, and replantation of extremities. These procedures involve preexisting pathophysiology or create pathophysiology that mandates that the anesthesia team must be well informed in order to provide appropriate routine, as well as resuscitative, anesthesia care. In the case of several procedures, such as liver transplantation and replantation of the extremities, the complications of lengthy surgery must also be considered and prevented.

The Guest Editor of this issue, Dr. Scott Wheeler, is a Professor of Anesthesiology, and has had extensive experience in establishing new anesthesia services or upgrading existing services in need of more

effective management. He is known in the anesthesia community as a "systems analyst," and is extremely well positioned to understand the subtle, but important, interactions between the various surgical subspecialties and the surgical procedures themselves. Dr. Wheeler has had significant experience as an editor, having previously co-edited two texts on anesthesia for complicated obstetrics. All of the authors of the articles on anesthesia for the special new operations that Dr. Wheeler has asked to contribute have had extensive experience in providing anesthesia for these new operations. Given the importance and timeliness of the subject matter, and the expertise of the authors and Editor, I think that this issue of *Anesthesiology Clinics of North America* will be a very valuable one to the reader.

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Kidney Transplantation

*Lois L. Bready, MD**

Over the past three decades, kidney transplantation has become a well-established therapy for renal failure. Advances in organ preservation, histocompatibility testing, and immunosuppression have enabled prolonged survival of both the allograft and the recipient, for both cadaveric and living related donor (LRD) renal transplants. Currently, there are renal transplant programs in university and community hospitals throughout the country. Approximately 10,000 renal transplants are performed annually in the United States,⁶⁷ and the list of patients awaiting cadaveric transplants is about 12,000.⁹² In this article, the surgical and anesthetic considerations relevant for the kidney recipient and the donor (living and cadaveric) will be described. Space limitation precludes the degree of detail available from other recently published sources.⁴⁴

HISTORY

Development of successful renal transplantation depended on the development of surgical techniques for vascular surgery. In 1902, Dr. Alexis Carrel described a technique for suturing arteries. That same year, Dr. Emerich Ullmann presented his experiments with kidney transplants in animals to the Surgical Society of Vienna. Carrel later developed the "Carrel patch," which enables anastomosis of even very small vessels, and completed numerous experiments with transplantation of kidneys, limbs, and hearts. In 1912 he became the first U.S. recipient of the Nobel Prize for Medicine, for his work on the suture of vessels and organ transplantation.

During the next couple of decades work continued on transplantation, and it was shown that kidneys transplanted in animals would function. Experimentation with xenografts (Table 1) had been performed by a number of investigators and continued into the 1920s. It became apparent that autotransplants functioned much longer than

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Table 1. *Types of Organ Transplants*

Autograft	Transfer of tissue/organ within same individual (for example, skin graft)
Isograft	Transfer of tissue/organ between genetically identical individuals (that is, identical twins), any tissues may be exchanged, with normal function and without need for immunosuppression
Homo/allograft	Transfer of tissue/organ between members of same species, with different genetic identities; most of current organ and tissue transplants (for example, kidney, liver, heart, cornea, bone)
Hetero/xenograft	Transfer of tissue/organ between members of different species (for example, dog to human, baboon to human)

allografts. Dr. Carl Williamson of the Mayo Clinic predicted the future determination of donor and recipient "reactions" and published photomicrographs in 1926 of the rejection reaction in the transplanted kidney.

By 1930, the Ukrainian surgeon Yu. Yu. Voronoy had performed renal transplants in dogs, using Carrel's vascular suture methods. Voronoy performed the first human renal cadaveric allograft in 1933 in the Ukraine; it was reported in 1936 in Spanish in *El Siglo Medico*.⁴⁵ The kidney was harvested several hours after death of the donor and was transplanted into the recipient's right thigh, under local anesthesia. The graft produced some urine, and the patient briefly improved but died about 48 hours later.

In 1954, the Peter Bent Brigham group performed the first renal transplantation between identical twins.⁷¹ The recipient received a continuous spinal anesthetic; the donor was anesthetized with ether. The recipient did well, married one of his nurses, and lived for 8 more years, without immunosuppression. By 1958, the Brigham group had reported seven twin-twin renal transplantations with good results.⁷⁹ Thus, the surgical technique of renal transplantation was able to evolve independently from the development of safe and effective immunosuppression.

Since the early days, the transplanted kidney has been positioned in the iliac fossa in adults. This location became the site of choice because the grafted organ "fits": it is small enough that it does not cause a great deal of abdominal enlargement or discomfort; the vascular supply is readily available, and vascular anastomoses can be performed without the need for vascular grafts; the transplanted ureter can be implanted easily into the native bladder; surgical access is more straightforward than the native location; and it obviates removal of native kidneys.

PRESERVATION

The renal allograft is optimally preserved and is associated with best function after transplantation when the surgeon avoids a pro-

longed period of ischemia at normal body temperature. This "warm ischemia time" should remain under 10 minutes, which one achieves by canulating the renal artery immediately after the kidney is removed and flushing the renal vascular system with preservative solution at 4°C. (This preservative solution contains potassium and is hyperosmolar, so it should be flushed out with an isotonic solution before the recipient receives the organ.)

Preservation of the kidney allows for transportation over great distances and for evaluation of potential recipients for preformed cytotoxic antibodies that would lead to immediate rejection of the graft (see following). Preservation techniques include simple hypothermic storage, which maintains good preservation for up to 48 hours; and pulsatile preservation, in which the organ is connected to a pump and the preservative solution is delivered in a pulsatile manner. This latter method may maintain good function up to 60 hours, but is more difficult and expensive.

HISTOCOMPATIBILITY AND IMMUNOSUPPRESSION

The ideal donor for a kidney transplant is a healthy identical twin with normal renal function. When such a transplant is performed, no immunosuppression is required, and the lifespans of graft, donor, and recipient are expected to be normal, as long as the original renal disease does not recur in the grafted kidney. Most anephric patients, however, are not fortunate enough to have an identical twin. Thus, their immune responses to foreign tissue must be anticipated and avoided, when possible, and pharmaceutically modified.

The introduction of histocompatibility testing brought about a significantly improved graft survival rate. It consists of two main components:

(1) Antigen-matching, in which an attempt is made to match major histocompatibility antigens. With a six major histocompatibility-antigen match, the outcome for LRD grafts improves by 15 to 30 per cent,⁸³ and for CAD grafts the improvement approximates 15 to 20 per cent.⁸⁴ Since the introduction of cyclosporine, however, graft survival rates may not be significantly better with well-matched donor-recipient pairs.^{38, 55}

(2) The presence of preformed cytotoxic antibodies of a prospective recipient against donor antigens bodes poorly for outcome of a graft. If the cytotoxic antibody cross-match is positive, the patient may well experience hyperacute or accelerated, acute rejection of the graft, and another recipient is usually sought.

Immunosuppression of the recipient follows the protocol of each transplant center. Most centers employ a regimen that includes cyclosporine A together with steroids, and may include azathioprine, as well as antithymocyte globulin or antilymphocyte globulin and monoclonal antibodies.

ANATOMIC AND PATHOPHYSIOLOGIC CONSIDERATIONS

Renal Anatomy and Physiology

The kidneys are paired retroperitoneal organs, derived from the metanephric blastema. Each kidney is supplied by a renal artery (usually single, but significant anatomic variation exists) that arises from the aorta. Each kidney receives about 10 per cent of the cardiac output (500 to 600 ml per min). The renal artery branches into interlobar, arcuate, and interlobular branches. The afferent arteriole enters the capillary network of the glomerulus and exits as the efferent arteriole. Each kidney normally contains approximately one million nephrons (Fig. 1). The vascular supply to the cortical nephrons differs from that of the juxtamedullary nephrons; the cortical nephrons have muscular, well-innervated afferent arterioles that usually contain juxtaglomerular cells (Fig. 2). Blood flows through the glomerular capillaries, and an ultrafiltrate of plasma collects within Bowman's space. Substances with molecular weights of 10,000 or less cross the glomerular capillary wall as easily as water and ions. Larger molecules are filtered less well, and proteins such as hemoglobin (molecular weight 68,000) and albumin (molecular weight 69,000) normally do not pass through the capillary wall. The filtered fluid flows through the various sections of the renal tubules, where excretion of water and solutes occurs.

The nerve supply to the kidneys is predominantly sympathetic and consists of branches from the celiac plexus, thoracic splanchnic nerve, lumbar splanchnic nerves, and the intermesenteric nerves.

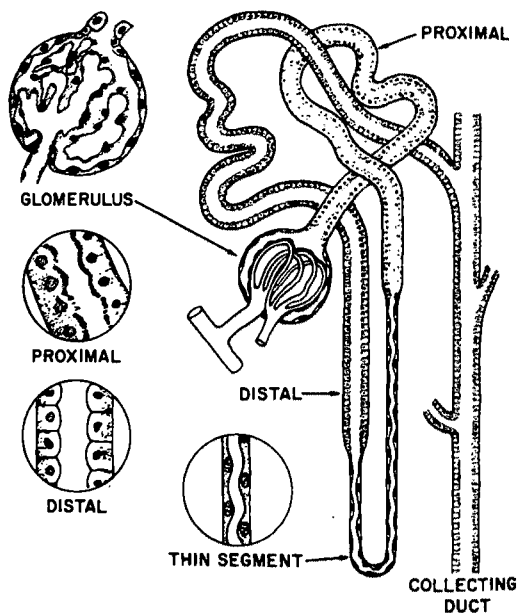


Figure 1. The composite parts of the nephron. (From Pitts RF: Physiology of the kidney and body fluids. Chicago, Year Book Medical, 1974, p 5; with permission.)

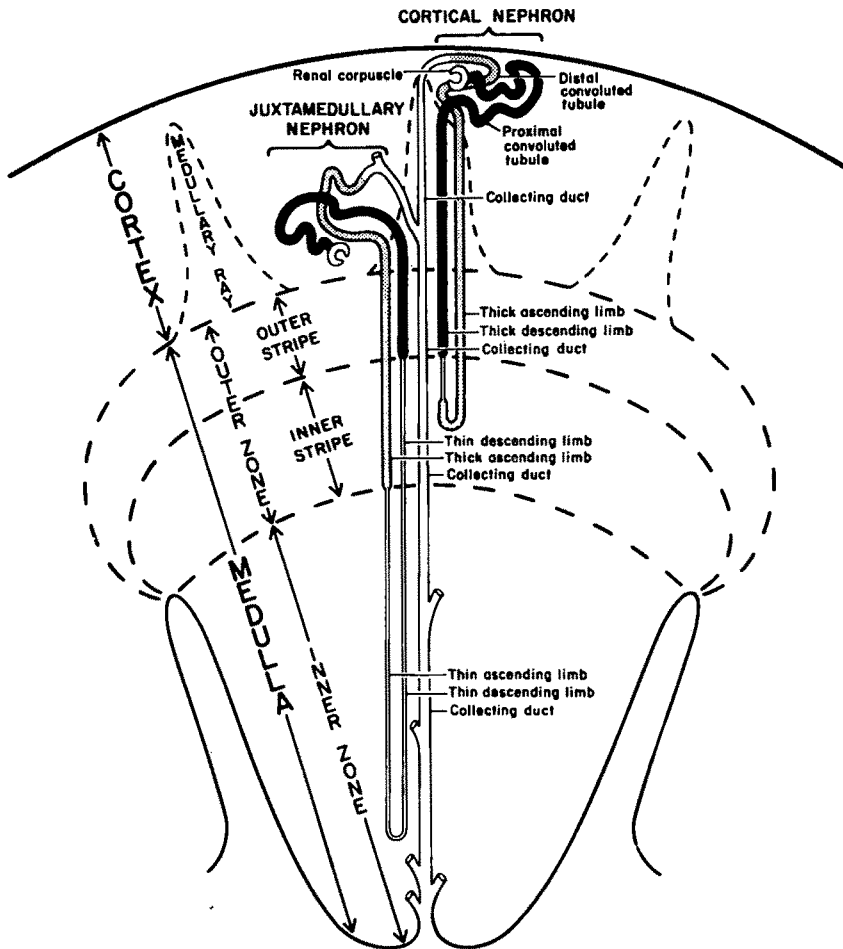


Figure 2. Schematic diagram of a cortical and a juxtamedullary nephron showing the relationship of nephron segments to zones of the kidney. (From Bulger RE: Kidney morphology. In Earley LE, Gottschalk CW (eds): *Strauss and Welt's Diseases of the Kidney*, ed 3. Boston, Little Brown, 1979, p 5; with permission.)

Neurogenic mechanisms are very important in the control of perfusion of the native (nontransplanted) kidney, but less so in the transplanted kidney. Manipulations that cause sympathetic stimulation (for example, cold, pain, pressure, fright, exercise, hypercapnia, hypoxemia) result in renal artery vasoconstriction.

Pathophysiology of Renal Failure

In renal failure, there is a permanent loss of functioning nephrons. Depending on the etiology, the loss of nephrons may be gradual or more rapid. In most series, the leading cause of end-stage renal disease

Table 2. *Stages of Chronic Renal Failure*

STAGE	CREATININE	GFR
1. Decreased reserve	Up to 2	>50
2. Renal insufficiency	2-8	25-50
3. Renal failure	8-20	10-25
4. Uremia	Over 20	<10
5. Dialysis	10-12	0

(ESRD) is glomerulonephritis, but other common etiologies include hypertension, diabetes, pyelonephritis, polycystic disease, and obstructive uropathy.

The remaining nephrons experience an increasing workload. Each nephron must handle more water and solute than normal; an osmotic diuresis occurs, and each nephron decreases its fractional reabsorption of sodium. This increases sodium excretion per nephron. Typically, a decreased ability to respond to sudden changes in salt and water intake occurs. Remaining nephrons finally can no longer respond normally to water and solute challenges, isosthenuria occurs, and other manifestations of uremia appear.

As renal function worsens, several stages of renal failure can be identified (Table 2), including the following:

Decreased Renal Reserve. There is up to 60 per cent loss of total nephron mass. There are usually no signs or symptoms during this stage, and the diagnosis may be made incidentally.

Renal Insufficiency. There is up to 90 per cent of renal function lost, resulting in decreased urinary concentrating ability and nocturia. Anemia and azotemia become apparent.

Renal Failure. There is less than 10 per cent of normal renal function; this is associated with progressive azotemia, usually severe anemia, acidosis, and electrolyte and fluid imbalance.

Uremia. Manifestations of uremia relevant to the anesthetist are listed in Table 3, all of which may increase the risks for the patient undergoing anesthesia and surgery.

Dialysis. As the patient's renal function deteriorates, a decision must be made by the primary physician regarding onset of dialysis. Choices include hemodialysis (HD) at home or at a center or continuous ambulatory peritoneal dialysis (CAPD). For either HD or CAPD, the patient will present to the operating room for placement of an "access," either a vascular shunt or cannula or a peritoneal catheter. These patients are among the sickest of our elective population; they frequently present as outpatients to minimize exposure to hospital-acquired infections, as well as costs. Dialysis improves many of the manifestations of uremia but may promulgate other problems (Table 4).

Table 3. Signs and Symptoms of Uremia**Behavioral, mental, or neurologic**

Depressive: fatigue, asthenia, malaise, shortening of concentration, memory defects, anorexia, drowsiness, suicidal thoughts, stupor, precoma, coma

Irritative: anxiety, fasciculations, twitching, headache, ataxia, asterixis, abnormal gait, vertigo, nausea, convulsions

Psychiatric: personality change, bizarre behavior, phobias, organic psychosis, selective amnesia, denial, kleptomania

Peripheral: pruritis, paresthesias, restless leg syndrome, monoplegia, paraplegia, sensory and motor defects, bladder atony and dysfunction

Ophthalmic: nystagmus, miosis, anisocoria, band keratopathy

Gastrointestinal

Membrane problems: glossitis, stomatitis, esophagitis, enteritis, pancreatitis, colitis, ileus

Functional problems: anorexia, dysgeusia, nausea, vomiting, hematemesis, constipation, diarrhea, abdominal distention

Structural problems: peptic and colonic ulceration

Cardiovascular-pulmonary

Pericarditis, acute and constrictive

Cardiomegaly

Pleuritis

Congestive heart failure

Change in blood pressure

Dysrhythmias

Vascular calcification

Accelerated atherosclerosis

Cheyne-Stokes and/or Kussmaul breathing

Hematologic

Anemia: normochromic, normocytic

Bleeding abnormality: prolonged bleeding time, abnormal platelet aggregation

Lymphopenia, mild thrombocytopenia

Metabolic

Hyperkalemia

Metabolic acidosis

Hypermagnesemia

Hyperphosphatemia

Hypocalcemia

Metastatic calcification

Medium sized arteries: arterial insufficiency, ischemia, skin ulceration, gangrene

Joints, sites of pressure: arthritis, decreased range of motion

Myocardium, skeletal muscle, lung

Musculoskeletal muscle pain and weakness, proximal myopathy, bone pain, bone fractures

Aseptic necrosis of bone

Disturbances in multiple endocrine systems

Carbohydrate intolerance

Hyperlipidemia

Gout and pseudogout

Wasting and abnormalities in protein metabolism

Immunologic

Reduced T-cell-mediated immune function

Impaired phagocytosis and chemotaxis

Atrophy of the lymphoid system including thymus

Reduced immune surveillance of neoplasia

Miscellaneous

Reduced wound healing

Hypothermia

Impaired response to pyrogen

From Schreiner GE: Uremia. In Massry SG, Glasscock RJ (eds): Textbook of Nephrology. Baltimore, Williams & Wilkins, 1983, p 452; with permission.

Table 4. *Impact of Dialysis Therapy on Clinical Manifestations of Uremia*

Dialysis improves the following manifestations of uremia:
Coagulopathy
Central nervous system abnormalities
Gastrointestinal symptoms (anorexia, nausea, vomiting, GI bleeding, diarrhea, hiccups)
Dialysis does not improve the following manifestations of uremia:
Peripheral neuropathies, autonomic neuropathy
Susceptibility to infection
Refractory (renin-dependent) hypertension
Anemia
Hemodialysis may produce the following abnormalities:
Rebound heparinization
Infections: hepatitis, HIV

PHARMACOLOGY OF RENAL FAILURE

Prediction of pharmacodynamics in the patient with renal failure (ESRD) can be one of the greater clinical challenges for the anesthetist. Serum albumin usually decreases, resulting in fewer albumin binding sites, which appear to have a lower affinity for protein-bound agents. This produces a greater unbound fraction of drugs, so that prolonged or exaggerated drug reactions occur with some frequency. Total body water usually increases in uremia, but it may be decreased in recently dialyzed individuals. Renally excreted compounds have prolonged half-lives, but the required loading dose may be unaltered. Overall, when selection of a non-renally excreted drug is possible, it probably represents the sensible course.

Depolarizing Muscle Relaxants

Succinylcholine is commonly used for the rapid sequence induction and is generally considered safe if the serum potassium is less than 5.5 mEq per L. It may bring forth an exaggerated hyperkalemic response in patients with advanced uremic neuropathy. When infused for longer than 2 hours in normal patients, the agent can produce a phase II block that is difficult to predict and treat.⁶⁸

Nondepolarizing Muscle Relaxants

Many patients with chronic renal failure have decreased muscle mass and may need a reduced total dose of muscle relaxants. The younger, healthier patients, however, may require doses of muscle relaxants similar to those given to normal healthy patients. In the absence of renal blood flow, the volume of distribution of nondepolarizing muscle relaxants is reduced, resulting in higher blood concentrations.⁶⁸

Atracurium. This agent has a short duration of action because it is broken down by both Hofmann elimination and nonspecific ester

hydrolysis.⁵² Duration and recovery are similar for ESRD and normal patients,^{36, 37, 51} and no cumulative effects have been demonstrated.⁵¹ Minor problems include histamine release with consequent hypotension following large doses and a temperature-related rate of degradation (for example, the hypothermic postoperative patient may have a longer lasting neuromuscular block). Clinically, there does not appear to be "cumulation" of effect, which makes dosing quite predictable and risk of postoperative effect unlikely.

Vecuronium. A monoquaternary homologue of pancuronium, vecuronium has significant biliary excretion.^{6, 11, 69} Although ESRD and normal patients react similarly to a single dose,³⁵ an increased duration of action follows 10 µg per kg increments in those patients with renal failure but not in normal people.¹¹ This potential "cumulation" could conceivably lengthen clinical neuromuscular blockade but has not produced major problems. Advantages of vecuronium include shorter duration of action, easier reversibility, and absence of cardiovascular effect. Some evidence exists for an apparent tolerance to vecuronium in patients with renal failure.⁶ With normal liver function and monitoring of neuromuscular function, however, cases of prolonged blockade occur infrequently.

D-Tubocurarine. D-Tubocurarine has been widely employed for renal transplantation,⁷⁶ largely because of its potential for hepatic excretion.²⁵ However, multiple doses may produce a prolonged terminal half-life.^{41, 91} Undesirable drug effects include ganglionic blockade and peripheral vasodilation, which may produce systemic hypotension. In 1976, Miller and Cullen⁷⁴ raised the question of recurarization with a report of acute postoperative respiratory failure in three patients with renal failure. In each case, the curare-induced neuromuscular blockade had been reversed, apparently adequately, before muscle weakness recurred. The second and third cases required reintubation and repeated anticholinesterase therapy. Postulated etiologies included relative overdosage of D-tubocurarine, potentiation of blockade by neomycin and by metabolic and respiratory acidosis, and inadequate reversal.⁷⁴

Pancuronium. This compound depends more on renal excretion than D-tubocurarine and has less biliary excretion.⁶⁸ Pharmacokinetic studies demonstrate a significant reduction of clearance and an increased volume of the central "distribution" compartment in patients with renal failure.^{68, 99} One finds considerable variability of clinical effect.^{10, 73} Measurement of the evoked mechanical twitch response concurrently with plasma levels of pancuronium confirmed that the prolongation of half-life in patients with ESRD was often but not always associated with an extended duration of neuromuscular blockade.⁹⁹ Prolonged neuromuscular blockade has been reported following its administration,^{1, 40, 96} and it is infrequently used in renal transplantation today.

Anticholinesterases

The elimination half-life of neostigmine is significantly prolonged in ESRD.²⁷ Similarly, pyridostigmine has a prolonged half-life of elim-

ination. In the renal transplant patient, however, pyridostigmine and edrophonium kinetics are like those in patients with normal renal function.^{28, 78}

Thus, when renal function is impaired, both skeletal muscle relaxants and anticholinesterases appear to be similarly affected, which provides a margin of safety against recurarization. Management of neuromuscular blockade may be made easier when immediate onset of diuresis follows transplantation. In those cases, both muscle relaxant and anticholinesterase will undergo rapid excretion.

Narcotics and Antiemetics

Don and others³² reported prolonged effects of narcotics in anephric patients. After single intravenous doses, mean plasma concentrations of morphine were significantly higher in patients with renal failure. Accumulation of morphine-3-glucuronide, the active principal hepatic metabolite, probably explains the increased sensitivity to morphine.² With immediate restoration of renal function, as in a successful renal transplant, there is no significant difference between the calculated, terminal morphine half-lives for controls and for transplant recipients.^{77, 94} A recent report¹¹¹ describes respiratory depression and elevated sufentanil levels in a patient with chronic renal disease.

Metoclopramide kinetics correlate with creatine clearance; hemodialysis does not effectively remove metoclopramide.⁶⁰ Cimetidine may have potential as an immunostimulatory agent.^{42, 82} This effect is not considered to be clinically significant by most transplant teams, but local preferences may vary.

Barbiturates, Sedatives, and Hypnotics

Thiopental is generally considered the induction agent of choice for patients with ESRD.¹⁰⁹ Altered protein binding (hypoalbuminemia, acidosis) might contribute to delayed emergence, although this is not a common clinical problem.¹⁸

Diazepam is metabolized by the liver, then the active metabolites are renally excreted.⁷ In renal failure, variable prolongation of sedative effect occurs. Emergence after induction with midazolam may also be delayed.¹⁰⁷

Diuretics

Potential of D-tubocurarine neuromuscular blockade by diuretics has been reported by Miller and coworkers.⁷⁵ They considered this to be a result of furosemide rather than mannitol by means of a direct depressant effect on the neuromuscular junction, a change in extracellular electrolyte concentration, or perhaps by altered redistribution of D-tubocurarine. Pharmacokinetic studies of furosemide reveal a marked fall in clearance.¹⁰³ A greater source of therapeutic misadventure may occur with mannitol, because large doses of mannitol (between 1.4 and greater than 2.6 g per kg) administered to patients in renal failure may produce hyponatremia.^{8, 14} Mannitol draws water into the extracellular fluid and then is poorly cleared by the

diseased kidney, or not cleared at all in the anephric patient, possibly producing cerebral edema and neurologic symptoms. Increased plasma osmolality may be calculated by the following equation:

$$\frac{\text{Grams of mannitol infused} \times 1000}{\text{Total body water} \times 182}$$

Acutely expanded intravascular volume may also result in congestive heart failure. In severe volume overload, dialysis may be required to remove the mannitol and fluid. Plasma potassium levels can also be affected by mannitol.²⁴

Antihypertensives and Antiarrhythmics

Antihypertensive drugs, including reserpine, hydralazine, alpha methyl dopa, and clonidine are frequently administered for hypertension in those with renal failure. Clonidine should be continued without interruption in order to avoid postoperative hypertension.

Sodium nitroprusside toxicity has been reported in a renal transplant patient.⁸⁹ Particular problems include lack of detoxification, impaired excretion of cyanide, the requirement for higher than normal doses of sodium nitroprusside to control hypertension, and the confusing picture of metabolic acidosis (owing to cyanide toxicity or to the underlying renal disease?).

Lidocaine pharmacokinetics and metabolism are not significantly impaired in renal failure.²⁶ However, the active metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) may accumulate.⁶³ Urinary excretion of procaineamide is proportional to creatinine clearance.⁶³ Quinidine undergoes hepatic oxidation, and is 80 per cent protein bound. The therapeutic concentration in renal failure does not exceed the normal range, and thus some prefer this agent to procaineamide in these patients.⁶³

Customary doses of propranolol can result in higher peak blood and plasma concentrations, and plasma clearance is significantly reduced. Propranolol is not cleared by dialysis.^{12, 63}

Calcium-Channel Blockers

Verapamil and nifedipine enhance the neuromuscular blockade of nondepolarizing relaxants.¹³ When indicated during the perioperative period, careful monitoring of neuromuscular function should be performed.

Immunosuppressant Therapy

Antilymphocyte globulin or antithymocyte globulin, administered for immunosuppression, may produce fever, which may result from allergic and anaphylactic-type reactions to equine or other animal-source globulins.⁸¹ Other complications secondary to immunosuppressant agents include hyperglycemia following high-dose steroid administration, and drug reactions to azathioprine or cyclosporine.

ANESTHETIC AND SURGICAL CONSIDERATIONS WITH THE RENAL TRANSPLANT RECIPIENT

Preoperative Evaluation and Preparation

The various manifestations of uremia must be considered (see Table 3). The patient's chart should be reviewed to determine the date of most recent dialysis treatment, post-dialysis electrolyte and hematocrit values, and the amount of weight lost or gained during the last dialysis. When dialysis immediately precedes the operation and produces a weight loss of more than 2 to 3 kg in the adult, significant hypovolemia is likely. Other preoperative concerns (apart from the customary preoperative evaluation of any patient presenting for surgery) include hypertension, anemia, coagulation problems, cardiovascular abnormalities, diabetes (and its degree of control), gastrointestinal abnormalities and the likelihood of aspiration, and immunosuppression.

Preoperative medication is individualized and aims to calm the frightened patient without producing undue depression. Meperidine is metabolized to normeperidine, which undergoes renal excretion. In people with renal failure, normeperidine accumulates, which may induce irritability, twitching, or seizures.³⁴ Thus, meperidine is not a good narcotic for these patients. Attention should also be given to pharmacologic modification of gastric contents, particularly in individuals with gastroparesis. Preoperatively, we usually give the insulin-dependent diabetic an increment of his or her customary dose of regular insulin and then monitor blood glucose intraoperatively. Antihypertensive medications should be given preoperatively if the patient has severe hypertension; additional blood pressure control may require intravenous antihypertensives during surgery.

Monitoring

Table 5 lists the customary monitors for the renal transplant recipient. Because the uremic patient becomes immunosuppressed both by his disease and by pharmaceuticals, procedures for invasive mon-

Table 5. Customary Monitors for Kidney Transplant Recipient

Stethoscope, precordial and/or esophageal
Electrocardiogram, preferably with printer
Arterial blood pressure, indirect and/or direct
Inspired oxygen concentration
Anesthetic circuit pressure
Oxygen saturation by pulse oximetry
End-tidal CO ₂
Urinary catheter
Temperature
Peripheral nerve stimulator (general anesthesia)

Other monitors may be employed if indicated by patient's medical condition.

itors and vascular access mandate use of a sterile technique. The relatively healthy individual, who possesses few medical complications and who has a short history of dialysis, may not require invasive monitors. When renal transplant patients are medically compromised, however, one should consider invasive perioperative monitoring.

The central venous pressure (CVP) catheter measures right heart filling pressures and provides venous access for blood sampling and administration of vasoactive drugs, especially when utilizing a multi-lumen cannula. Monitoring CVP during renal transplantation is routine in most transplant centers. Most transplant protocols require fixed intravenous doses of colloids, crystalloids, and osmotic diuretics (mannitol), but the appropriate doses of these substances are determined by their effects on intravascular volume and CVP. If the patient is positioned in Trendelenburg's position, the absolute CVP value may carry less significance than the direction or trend of change.

Routine monitoring and manipulation of pulmonary artery pressures (PAP) may improve postoperative function of cadaveric grafts.^{20,64} For example, when the mean PAP exceeds 20 mm Hg and the PA diastolic pressure exceeds 15 mm Hg, the incidence of acute tubular necrosis falls to one-sixth that of patients with lower filling pressures. At many transplant centers, however, PA catheters are not inserted unless a strong suspicion of poor left ventricular function or a significant disparity between right and left ventricular function exists, because of the concern for sepsis and other potential sequelae.^{49, 95}

Some diversity of opinion exists regarding the use of indwelling arterial catheters for intraoperative monitoring of renal transplant patients. Opponents cite the risk of damage to the radial artery, which might subsequently render it unsuitable for a vascular access. However, the ability to continuously monitor blood pressure may be necessary.¹⁰¹ Autonomic insufficiency and abnormalities of blood pressure regulation are common, and many patients are chronically hypertensive.³ Intra-arterial pressure monitoring may be more accurate than indirect methods when arterial calcification is advanced, and the arterial pressure waveform allows visual interpretation. Beat-to-beat analysis of the arterial pressure tracing in conjunction with a continuously monitored electrocardiograph assesses the electromechanical function of the heart and the patient's overall hemodynamic performance.⁴³ Additionally, immediate postoperative management of the awakening renal transplant patient (who often becomes quite hypertensive during emergence) is facilitated by continuous arterial pressure monitoring.

When 22 to 20 gauge arterial catheters are inserted sterily by the skilled practitioner, a low incidence of complications follows in adults⁹⁷ or in children.⁶⁶ In renal patients, the physician must individually select the best placement site for the arterial catheter. When a vascular access exists in one upper extremity, we usually cannulate the radial artery of the other upper extremity. If both upper extremities have a vascular access, alternate arteries include the dorsalis pedis, posterior tibial, axillary, and superficial temporal. In a lower extremity

cannulation, one utilizes the limb contralateral to where the kidney will be transplanted, since occlusion of the iliac artery (for vascular anastomosis) proximal to the arterial line dampens or obscures the pressure tracing during surgery. In case of a nonfunctioning arteriovenous graft in the upper extremity, retrograde flow from the ulnar artery through an intact palmar arch may produce a palpable radial pulse. Catheterization is unlikely to be fruitful, however, if the radial artery is permanently occluded above the pulse. The axillary artery represents a good site, because of its large caliber, proximal position, and its location well away from the customary sites for arteriovenous access. As stated, insertion methods and the dressing must comply with accepted standards of sterile technique.⁵⁰

Choice of Anesthesia

Renal transplantation often requires several hours of anesthesia and occasionally causes significant blood loss. The first twin recipients received continuous spinal anesthetics.¹⁰⁵ Regional anesthesia (spinal or epidural) continues to be popular with some anesthetists.^{61, 70} Advantages of regional methods, particularly before routine preoperative dialysis became customary, included peripheral vasodilation to decrease afterload, excessive preload, and myocardial work; avoidance of tracheal instrumentation; and little exposure to anesthetic drugs primarily cleared renally. Possible contraindications to regional anesthesia include coagulopathy (uremic or secondary to heparin) and an unpredictable duration of surgery. With improved preoperative patient preparation, newer anesthetic drugs having less dependence on renal excretion, and with improved monitoring, general anesthesia can also be applied with great safety. Either method of anesthesia, applied skillfully, safely, and reliably meets the needs of patient, surgeon, and anesthetist.

This author prefers general anesthesia for most transplant recipients. Most patients are premedicated with oral diazepam, metoclopramide, ranitidine, and sodium citrate in appropriate doses. Induction is with thiopental and fentanyl, lidocaine is administered intravenously prior to intubation under cricoid pressure, and intubation is facilitated with succinylcholine or atracurium. If succinylcholine is contraindicated, muscle relaxation is afforded by atracurium or vecuronium. Isoflurane is a satisfactory primary anesthetic agent, provided that the patient tolerates any resulting tachycardia and hypotension; if the thrill of the patient's vascular access diminishes, the agent is discontinued and the technique is altered to a balanced anesthetic with intermittent boluses of fentanyl. Maintenance of neuromuscular blockade is with infusion atracurium. Concern about possible nephrotoxicity of enflurane speaks against its use.

Intraoperative Considerations

Whether the transplanted kidney comes from a relative or from a cadaver, the surgical procedure for renal transplantation is similar. To implant the kidney, the surgeon first anastomoses the renal vein, then

the renal artery, and finally the ureter. After anesthesia has commenced, a member of the patient care team sterilely inserts a Foley catheter and distends the bladder with a saline-Betadine (or antibiotic) mixture to lessen the risk of wound infection. The urinary catheter is clamped and the collecting bag is passed to the head of the table. Obviously, no urine will flow until later in the procedure, after the kidney has been transplanted and the catheter has been unclamped. The patient's abdomen is prepared and draped, and the surgeon makes an incision in the right or left lower quadrant (the small child may require a midline incision, with vascular anastomoses to more proximal arterial and venous supply, the aorta and vena cava). He or she then elevates the muscle and fascia to develop a pocket in the iliac fossa, over the iliac vessels. Many surgeons employ a self-retaining retractor to hold the wound open during the procedure. Although good surgical access does not require profound muscle relaxation, the patient must not move during the creation of the delicate vascular anastomoses, lest they be damaged. Monitored neuromuscular blockade is recommended. Vascular anastomoses are individualized depending on the anatomy of the graft and recipient vessels (Fig. 3), but are

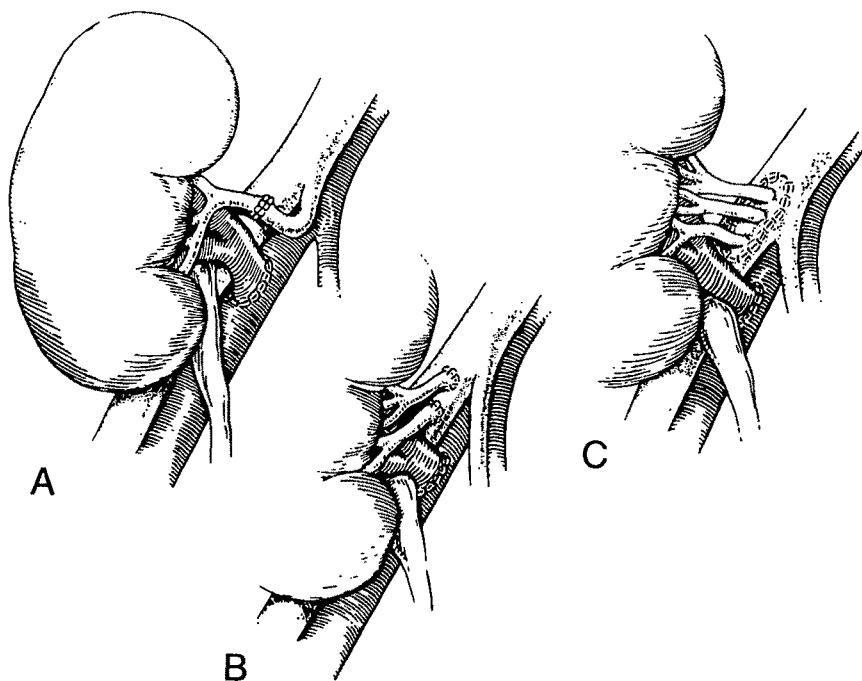


Figure 3. Techniques of re-establishing the allograft's vascular supply. (A) Renal artery to internal iliac artery. (B) Anastomosis of multiple renal arteries to the external iliac artery. (C) Carrel patch anastomosis to external iliac artery. (From Whelchel JD: Surgical aspects of renal transplantations. In Graybar GB, Bready LL (eds): *Anesthesia for Renal Transplantation*. Boston, Martinus Nijhoff, 1987, p 90; with permission.)

usually performed in the following order: (1) allograft renal vein to the recipient's proximal external iliac vein; (2) if the allograft has one renal artery, it is anastomosed to the recipient's internal iliac artery. If the graft has multiple arteries and comes from a relative (that is, there is no cuff of donor aorta for a Carrel patch), multiple anastomoses are made to the external iliac artery. Grafts from a cadaveric donor with a cuff of donor aorta are anastomosed to the external iliac artery. Numerous or complex vascular anastomoses require much longer surgical times.

Circulating blood volume and systemic pressure must be normal or slightly greater than normal at the time of revascularization to ensure adequate perfusion of the graft. When indicated, the expansion of circulating blood volume with crystalloid or colloid necessitates careful monitoring. As described earlier, large doses of mannitol may yield significant alterations of serum sodium and potassium, indicating electrolyte measurements. When the vascular clamps are opened, the graft should become pinker and firmer, and urine may begin to emerge from the cut end of the ureter. The ureter is then connected to the bladder or to the recipient's ureter, although an ileal conduit may be required if there is not a functioning bladder. (The ileal conduit may be created at the same time as transplantation, but is often performed as an earlier procedure.) The urinary catheter is unclamped, final inspection for vascular integrity is performed, and the wound is closed.

Hyperkalemia may complicate intraoperative management of the renal transplant patient,⁴⁸ particularly in diabetics who can have unpredictable increases in serum potassium.^{23, 47} Transplantation of kidneys with their adrenal glands intact (from cadaveric donors) has resulted in acute hemodynamic changes (hypertension, ventricular tachycardia, sinus bradycardia), probably from release of catecholamines.³⁹

Postoperative Management

Pharmacologic and hemodynamic alterations make the postanesthetic care of the recipient somewhat different from "routine" postoperative patients. It may be helpful to divide this patient population into "low risk" and "high risk" groups.⁵³ The first group, the otherwise healthy patient with ESRD, is generally younger and has recently contracted ESRD. They generally do well postoperatively and may be recovered in a recovery room. The second group includes individuals who often have diabetes, pancreatitis, hypertension, uremia, a past history of a gastrointestinal bleed, and/or coronary artery disease, and they often exceed 50 years of age.⁵³ They require intensive postoperative care and invasive monitoring, which can best be provided in an intensive care unit.

Postoperative analgesia is tailored to individual requirements. Epidural narcotics can provide excellent analgesia. Occasionally, other surgical procedures are performed along with renal transplantation (for example, nephrectomy, splenectomy, ileal conduit). These

cases induce significantly more postoperative pain, increasing the requirements for postoperative analgesia.

A variety of common anesthetic sequelae may surface postoperatively. Knowledge of common problems that may present in the post-anesthetic period facilitates immediate recognition and prompt management. The lupus patient on steroids may have loose, brittle teeth that are easily broken or dislodged. Sufficient care must be taken with padding, positioning, and patient protection. Clotting of the arteriovenous graft occurs commonly^{15, 46, 62}; thus, continued protection of the vascular access and periodic evaluation for a thrill are recommended perioperatively.

The self-retaining retractor employed for exposure of the iliac fossa may compress the femoral nerve, leading to *femoral neuropathy*, with loss of flexion of the hip and extension of the knee owing to quadriceps femoris palsy. Also, sensation and autonomic function are diminished over the anterior aspect of the thigh and medial and anteromedial aspects of the calf.^{16, 115} Rapid resolution of this neuropathy is the rule. *Brachial plexus palsy* occurs infrequently, but the recipient carries increased risk for the injury because of the following factors: hypovolemia, hypotension, arteriosclerotic cardiovascular disease, electrolyte imbalances, diabetes mellitus, coagulopathy, and hypothermia. Surgical positioning may require abduction of the patient's arms to greater than 90 degrees, and, if so, positioning of the arms on wedge-shaped supports reduces stretch of the brachial plexus. Arm or hand pain may also relate to the vascular access. For example, arteriovenous shunting may produce ischemia of the distal arm and hand if little collateral flow remains. This "steal" syndrome¹¹² may easily be confused with neural trauma associated with malpositioning. Revision of the vascular access may be required to relieve pain.

ANESTHETIC AND SURGICAL CONSIDERATIONS WITH THE LIVING RELATED DONOR

LRD transplants average approximately 25 per cent of all renal allografts in the United States, although the percentage varies widely.¹⁰⁸ In comparison to success rates in cadaver transplants, the survival rates of LRD kidneys are not improved as significantly by the new immunosuppressive drugs, for example, cyclosporine.¹⁰² With LRD renal transplantation, the surgery can be scheduled electively, enabling thorough medical evaluation and preparation of both donor and recipient. The allograft is generally a healthy, functioning, anatomically normal kidney. Furthermore, the circumstances surrounding its retrieval are more controlled, and the warm ischemic interval is likely to be shorter than with a cadaveric graft. Although it would be desirable not to subject the LRD to the potential morbidity and mortality of donor nephrectomy, the supply of cadaver renal allografts in the United States is insufficient.²¹

Preoperative Evaluation and Preparation

The candidate for kidney donation should be in good health, without evidence of acute or chronic illness, and free of renal disease or hypertension. Common exclusion criteria include myocardial infarction within the previous 6 months, acute or chronic liver disease, gastrointestinal malabsorption, a recent history of malignancy,⁹⁸ and diabetes mellitus.¹⁹ Patients at the extremes of age are not usually accepted, although occasional exceptions are made. Minor children may serve as LRDs under special circumstances such as donation to an identical twin.³³

Fluid Management. Most renal transplant programs employ a protocol for perioperative management of intravenous fluids, to ensure optimal renal blood flow and adequate urine output. The transplant team initiates an intravenous line the night before surgery, followed by varying rates of fluid administration, generally a balanced salt solution.^{4, 31, 80} Najarian's protocol, which, at the time represented a major departure from customary preoperative preparations, called for 15 ml per kg of 5 per cent dextrose in 0.45 per cent saline solution given at least 1 hour before induction of anesthesia, with a goal of 1.5 ml per minute urine output.⁸⁰ Currently, most protocols are similar. Mannitol, 12.5 to 25 g IV, is given when surgical manipulation of the kidney begins and if urine output decreases. The presence of oliguria prior to induction of anesthesia dictates delay of the nephrectomy until urine output has increased.

Premedication. Premedication aims to make the donor calm, tranquil, and amnesic, without producing hemodynamic compromise. Virtually all premedicants have been employed preoperatively in the renal donor.⁴ However, specific considerations such as likelihood of histamine release (and consequent vasodilation, venous pooling, and hypotension) and antidiuretic effect^{9, 113} make morphine less suitable. Similarly, drugs with alpha-blocking properties (for example, droperidol) might contribute to intraoperative hypotension associated with the nephrectomy position. On the other hand, alpha-blockade may protect against the renal vasoconstriction associated with sympathetic stimulation.⁹ In a healthy well-hydrated patient, these agents do not usually cause problems. Yet, their potential effects should be considered in the planning and selection of premedication.

Monitoring. Standard monitoring for the healthy nephrectomy patient includes electrocardiogram, indirect blood pressure, auscultation of heart sounds with precordial/esophageal stethoscope, oxygen saturation by pulse oximetry, end tidal capnography, core temperature, and urine output. On occasion, invasive monitoring with CVP or indwelling arterial catheter may be employed, although the indications for their use are infrequent in these healthy patients. Due to possible alterations of respiratory and hemodynamic function (see following), this author emphasizes the use of some means of following oxygenation and ventilation (for example, pulse oximetry, end tidal gas monitoring).

Anesthetic Management

Because of the respiratory and hemodynamic effects and bodily discomfort imposed by the flank position, general anesthesia is most commonly chosen. After placement of monitors and measurement of baseline vital signs, anesthesia is induced and the trachea intubated. Induction agents and muscle relaxants are selected according to the needs of the patient and the preferences of the anesthetist, with consideration given to maintenance of hemodynamic stability. Thus, agents that promote significant vasodilation and venous pooling should be avoided. It is advisable not to administer large doses of drugs that are primarily excreted renally, because renal reserve decreases post-nephrectomy, possibly leading to prolonged drug elimination. Maintenance anesthetic agents are selected to provide a satisfactory anesthetic and to maintain hemodynamic stability. This author finds a technique employing nitrous oxide, oxygen, narcotic, and muscle relaxant to be safe and effective. Neurolept anesthesia may be associated with decreased urine flow, increased urine concentration, and decreased solute excretion, but similar effects can be seen with potent inhalation agents.⁹ Inhalation agents are widely used for LRD nephrectomy.^{4, 106} All of the volatile agents cause some reduction of renal blood flow and glomerular filtration rate apart from the effects of surgical stimulation.⁹ Potentially nephrotoxic inhalational agents (for example, methoxyflurane) should be avoided. Regardless of agents chosen, one should control ventilation to provide eucapnia, since hyperventilation and hypoventilation may cause renal artery constriction.

Donor nephrectomy usually takes place through a subcostal flank incision, with the patient positioned in either a flank ("nephrectomy" or "kidney") position or prone. Appropriate equipment and padding should be readily available for the planned approach.

Before moving the patient into the flank position, the urinary catheter is inserted (if not already in place); the legs may be wrapped with compressive bandaging or stockings to protect against venous pooling in the lower extremities; and other intravenous or monitoring lines are inserted as needed. Passage of a gastric tube is possible during the flank position, but is more easily accomplished in a supine patient. Finally, to avoid the hemodynamic instability associated with a position change during deep anesthesia with a potent inhalational agent, one can maintain anesthesia primarily with N_2O/O_2 and muscle relaxants until the patient is repositioned and hemodynamically stable.

The kidney position is established by moving the anesthetized patient into the lateral position, with the flexion point of the operating table at the level of the iliac crest (Fig. 4). This position allows optimum surgical exposure during the nephrectomy without directly compressing the thoracic cage. Flexion of the lower leg at the knee and the hip to 90 degrees, with a pillow placed between the legs, provides stabilization. The table is then flexed until the muscles of the flank are taut, and the kidney rest is raised for further flexion, if

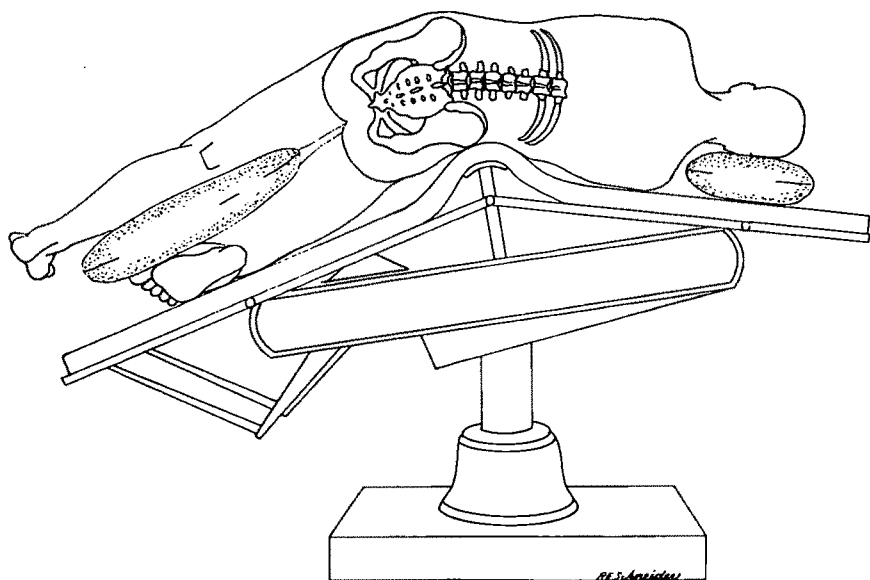


Figure 4. The kidney rest is positioned beneath the iliac crest, the optimal position. (From Kropp KA: Unusual positions. Surgical requirements: Urology. In Martin TJ (ed): Positioning in Anesthesia and Surgery. Philadelphia, Saunders, 1978, p 162; with permission.)

necessary. This position often impairs venous return. Wrapping the lower extremities and making changes in position slowly (with frequent pauses to evaluate blood pressure) helps to minimize severe impairment of venous return. Extreme flexion may attenuate cardiac output via compression of the abdominal aorta. When using tape to secure the patient, one must avoid bony prominences (for example, the head of the femur) and compression of the abdomen. The upper arm may be supported on stacked pillows, a padded Mayo stand, or (preferably) an "airplane" support, which is then adjusted to prevent compression of the patient's face, thorax, bony prominences, or peripheral nerves.

Proper padding of the head is essential. The head is supported so that the cervical spine remains aligned with the thoracic spine, and the dependent ear and eye are protected from direct pressure. In the patient with very broad shoulders, padding of considerable height may be required. Improper support of the head impairs venous drainage of the head. Furthermore, transient Horner's syndrome has occurred in a patient who underwent prolonged surgery in the kidney position (Fig. 5). Proposed mechanisms included a stretched and ischemic cervical sympathetic chain.⁵⁴ The axillary contents may be compressed when the lower arm remains directly under the thorax, possibly injuring the brachial plexus.⁴ One prevents this by moving the lower arm anterior to the thorax and placing an axillary roll. Then, radial artery palpation rules out axillary artery compression. Reassessment of breath sounds confirms proper tracheal tube position.

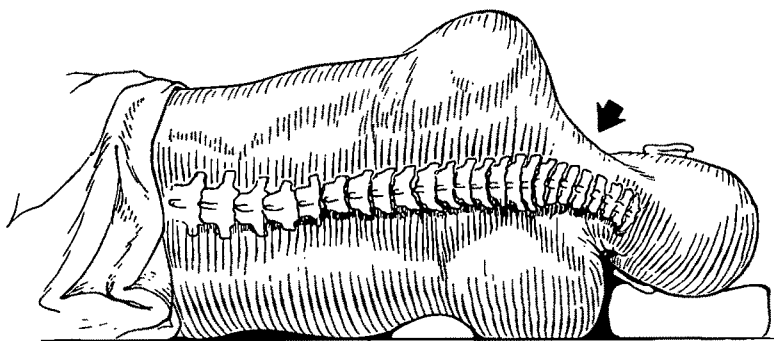


Figure 5. Inadequate support of the head produces misalignment of cervical and thoracic vertebrae (arrow). (From Jaffe TB, McLeskey CH: Position-induced Horner's syndrome. *Anesthesiology* 56:49, 1982; with permission.)

Respiratory Effects of the Flank Position

Gravity influences the pulmonary blood flow, which preferentially distributes to the dependent lung.^{30, 65, 114} However, positive pressure ventilation together with muscle relaxation enhances expansion of the upper lung.^{5, 56, 90} The reduced functional residual capacity in the dependent lung leads to airway closure and alveolar collapse.⁵⁹ The resultant V/Q mismatch leads to decreased oxygenation. In addition, the relative hyperperfusion and hypoventilation of the dependent lung, in combination with hypervolemia, may produce unilateral pulmonary edema of the dependent lung.¹⁰⁰

Additionally, the nephrectomy position adversely affects thoracic compliance; total compliance decreases by 17 per cent with an elevated kidney support.⁸⁷ Vital capacity and tidal volume also decrease.²² The detrimental respiratory effects of the flank position may worsen with time, indicating continued vigilance.

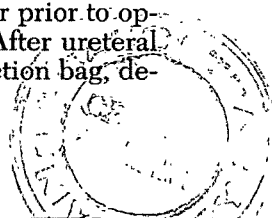
Not uncommonly, pneumothorax develops during nephrectomy.^{4, 104, 108} Recognition is important, and N₂O should be discontinued to avoid expansion of the pneumothorax. At the conclusion of the procedure, the anesthetist maintains inflation of the patient's lungs while the surgeon closes the pleura. On occasion, thoracostomy tube drainage is necessary. In the absence of lacerated pulmonary parenchyma, however, there should not be a continuing air leak, and simple needle aspiration may resolve the pneumothorax.

Obvious facial and conjunctival edema are common after administration of large volumes of crystalloid fluid to patients positioned for nephrectomy.⁴

Intraoperative Considerations

Many transplant surgeons prefer to divide the ureter prior to operative dissection of the donor kidney and its vessels. After ureteral division, urine output, as measured in the urinary collection bag, de-

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creases. Although this approach allows for minimal warm ischemic time for the allograft, some surgeons prefer to divide the ureter after vessel ligation. Local anesthetic may be applied to the renal vessels, once dissected, to minimize the vascular spasm resulting from manipulation. Many LRD protocols call for heparinization.

As mentioned earlier, optimum circulating blood volume is essential. If hypotension occurs, volume expansion with crystalloid and colloid is preferred to administration of vasopressors. Alpha-agonists constrict the renal arteries and, thus, may produce renal hypoperfusion, possibly contributing to acute tubular necrosis and failure of the grafted kidney. Low-dose dopamine enhances renal blood flow and is favored by some clinicians.⁵⁷ Adequate preoperative hydration usually prevents intraoperative oliguria. Low urine output necessitates fluids and osmotic diuretics. In case of sudden oliguria or anuria, mechanical obstruction of the urinary catheter should be considered.

Potential Intraoperative Problems

Surgical Problems. In donors, intraoperative surgical difficulties have included bleeding requiring reoperation, splenectomy, and adrenalectomy.¹⁰⁸ Other operative complications of the nephrectomy/flank position include ligation of the contralateral renal vein with consequent renal failure (in an infant)⁷² and rhabdomyolysis (owing to compression of the buttock by the kidney rest for 4.5 hours).²⁹ Imperfect hemostasis can be associated with considerable blood loss. When the lumbar approach is employed, the vascular pedicle to the kidney is deep and obscured by perinephric fat, making surgical control of hemorrhage difficult. Because each kidney receives 10 per cent of total cardiac output, unsecured vascular trespass can lead to exsanguinating hemorrhage. Dr. Vandam's description of the first LRD renal transplant in Boston included the following description regarding management of the healthy donor: "Anesthesia and operation proceeded uneventfully until a hemostatic clamp applied to the aorta lost its grip with resulting brisk but brief hemorrhage."¹⁰⁶ He remarked that the wisdom of placing two large bore intravenous catheters became rapidly apparent. In one large series of donor nephrectomies, operative blood loss exceeded 500 ml in 156 of 628 donors (25 per cent); blood was transfused in 75 (12 per cent).¹⁰⁸ In contrast, Aldrete's series⁴ noted that only 7 of 238 donors (3 per cent) required blood transfusion.

Anesthetic Problems. Intraoperative anesthetic problems reported include difficult intubation, hiccups, vomiting, and poorly controlled airway reflexes.⁴ Because donors represent a diverse group of patients, it is reasonable to expect that common and life-threatening anesthetic difficulties can be encountered. Thus, anesthesia should be managed by experienced anesthesia personnel.

Postoperative Management

During the immediate postoperative period, the possibility of pneumothorax warrants a routine chest radiograph immediately after

nephrectomy. Incisional flank pain causes splinting with reduced tidal volume and the potential for atelectasis. Possible alternatives for good analgesia include a patient-controlled analgesia device, a regional method (intercostal, subcostal, or epidural block with local anesthetic or opioid), and/or transcutaneous electrical nerve stimulation. Following use of loop diuretics, hypokalemia can occur requiring correction. Also possible are ileus and gastric dilation, which result from intra-peritoneal manipulation and indicate gastric drainage.

ANESTHETIC AND SURGICAL CONSIDERATIONS WITH THE CADAVERIC DONOR

Preoperative Evaluation

Most transplanted kidneys come from cadaveric donors. The best preserved organs are from "heart-beating donors," (that is, brain dead subjects with stable hemodynamics and adequate respiratory parameters). In contrast, organs harvested after cardiopulmonary arrest endure a longer warm ischemia time and are associated with a higher incidence of post-transplantation failure.

Indeed, the advent of organ transplantation necessitated well-defined criteria for brain death. To avoid a conflict of interest, members of the transplant team should not participate in the declaration of brain death of a prospective organ donor.

The selection of a donor requires the following criteria: (1) brain death; (2) an age of 1 to 65 years; (3) normal renal function; (4) no history of hypertension or insulin-dependent diabetes mellitus; (5) the absence of active infections or communicable diseases; and (6) no malignancy besides primary brain tumor or nonmelanoma skin carcinomas. Multiple organs are frequently harvested from a cadaveric donor, which requires the coordination of various surgical teams (often from multiple centers).

Preanesthetic evaluation focuses on optimization of hemodynamics and circulating volume. Because many cadaveric donors have received therapy for intracranial pathology, dehydration may exist from use of diuretics. Also, few vascular access sites may remain. Thus, additional intravenous catheters should be considered and a CVP catheter may be helpful. One must keep the patient normovolemic to mildly hypervolemic before harvesting begins. A guideline for adult donors is the "Minimum Hundreds Criteria"⁸⁵: systolic blood pressure greater than 100 mm Hg; PaO₂ greater than 100 mm Hg; and hourly urine output greater than 100 ml. The anesthesia team may need to give crystalloid, colloid, or even blood for stable hemodynamics. Low-dose dopamine augments urine production, but may be deleterious to the function of a donated heart. Therefore, if other organs are to be procured, consultation with the other harvest teams is recommended prior to the use of vasoactive agents.

Anesthetic management of the cadaveric donor is straightforward.

No anesthetic agents are needed, but neuromuscular blockade is required. Respiratory support entails positive pressure ventilation with an FIO_2 of 1.0, for a normal end-tidal CO_2 and a high oxygen saturation, as measured by pulse oximetry. As with living donors, mannitol and furosemide are given according to protocol, and heparin administration precedes organ harvesting. The kidneys are removed en bloc with ureters while the vessels remain attached to portions of aorta and vena cava. Following removal of the organs, ventilation is disconnected and anesthetic support ceases. Other tissues may still be harvested (for example, skin, corneas, bone) after cessation of ventilatory and circulatory support.

SUMMARY

In summary, renal transplantation is an effective therapy for ESRD, which is performed commonly throughout the United States. Appropriate consideration for the altered physiology and pharmacology of the uremic patient, together with knowledge about intraoperative management, enables improved patient care and optimum outcome.

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Anesthesia and Pancreatic Transplantation

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Because of the marked improvement in graft survival rate, the exponential increase in the number of pancreatic transplants being performed annually promises to continue for the foreseeable future. Advances in organ preservation, surgical technique, and immunosuppression account for this recent improvement. Until a medical cure is found, pancreatic transplantation offers the only hope of eradicating type I diabetes mellitus (DM) and preventing the progression of its devastating complications.

Kelly and Lillehei⁸⁵ performed the first human pancreatic transplant in 1966 at the University of Minnesota. The first decade of clinical pancreatic transplantation resulted in dismal statistics. One-year graft survival was 5 per cent, and patient survival was 41 per cent (Fig. 1). From 1983 through March 1988, the worldwide 1-year graft survival rate increased to 46 per cent associated with 82 per cent patient survival.¹⁴³

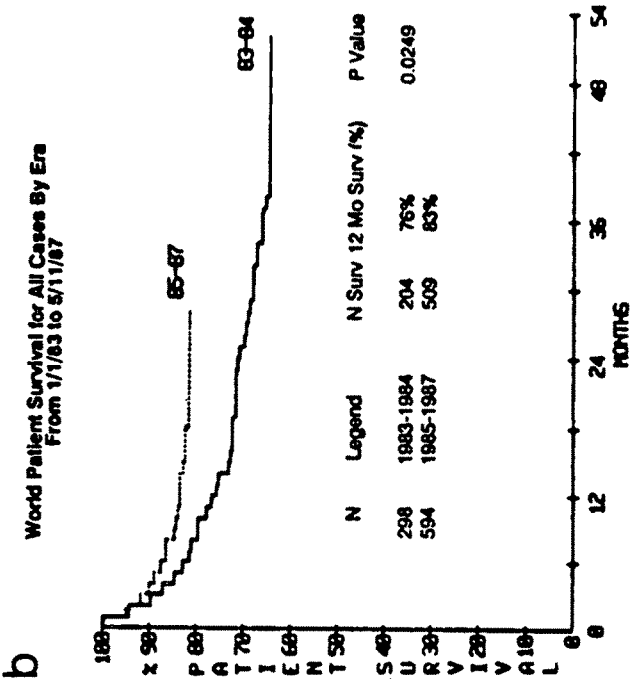
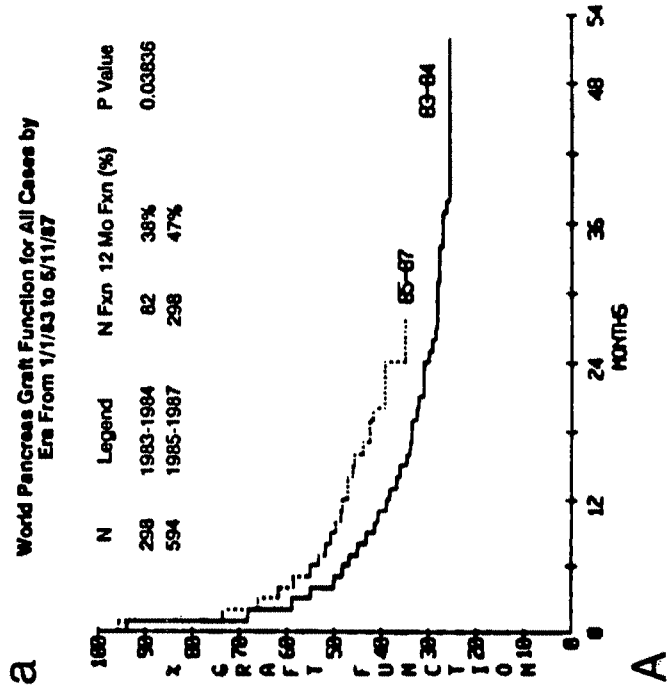
Two centers with extensive experience, the Universities of Minnesota and Wisconsin, recently reported 1-year pancreatic graft survival rates of 86 per cent and 87 per cent, respectively, when performed as a combined procedure with renal transplantation.^{136, 145} Other transplant centers with less experience have published equally encouraging data.^{39, 90} Thus, the "center effect" that has been one of the most important factors in renal graft survival may not be as apparent for pancreatic transplantation.¹⁰⁰ Or interpreted otherwise, good transplant centers will continue to have good results in other areas of transplantation.

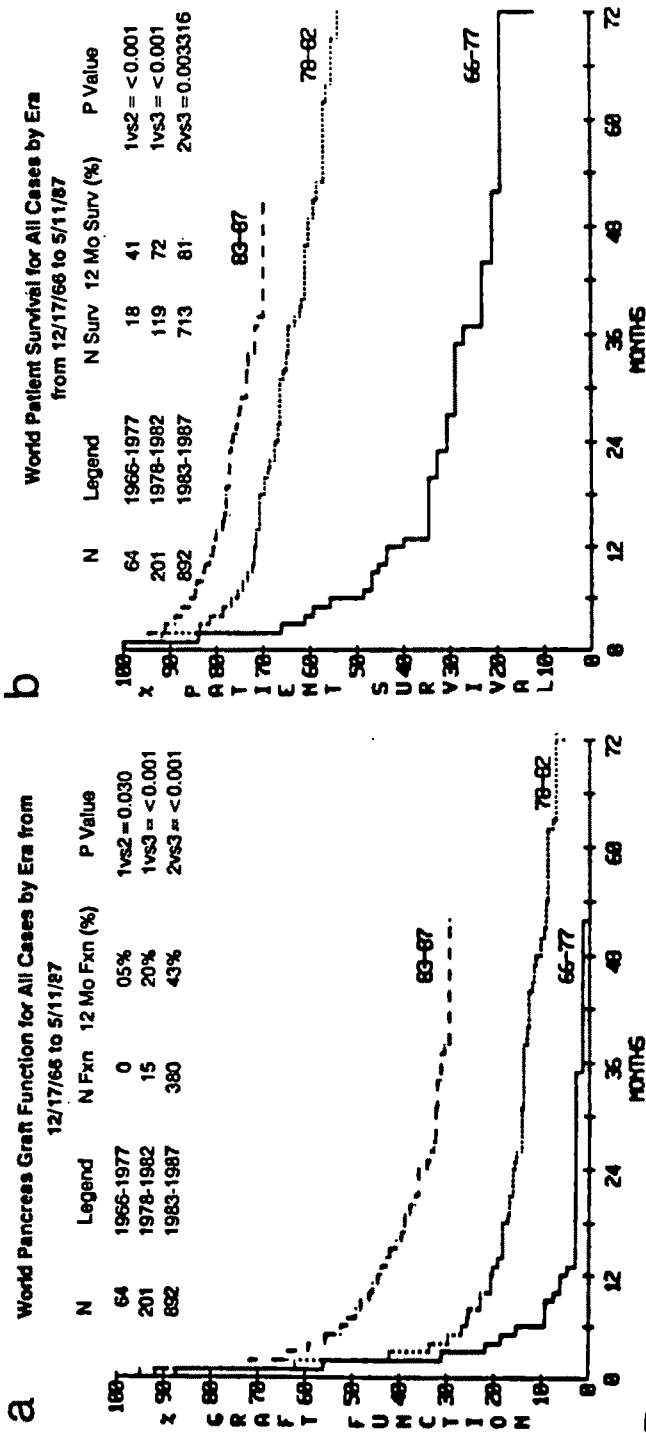
Sutherland stated that "pancreas transplantation is indicated when the already present or expected complications of type I diabetes will exceed the expected complications of transplant surgery and long-

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B Figure 1. Worldwide data from the Pancreatic Transplant Registry reveal improvements in both, A, graft survival (insulin-independence) and patient survival, B. The lower two graphs depict 1985 to 1987 statistics were significantly better than 1983 to 1984. (From Sutherland DER, Moudry KC: Report of the International Transplant Registry. In Terasaki PI (ed): Clinical Transplants. Los Angeles, UCLA Tissue Typing Laboratory, 1987; with permission.)

term immunosuppressive therapy.”¹⁴² Combined pancreatic and renal transplantation has become the optimum therapy for the type I DM patient with end-stage renal disease (ESRD).⁹⁹ Whether earlier pancreatic transplantation can prevent the microangiopathic complications associated with type I DM, including nephropathy, retinopathy, and neuropathy as well as the macroangiopathic accelerated arteriosclerosis is receiving active investigation.

PATHOPHYSIOLOGY OF TYPE I DIABETES MELLITUS

The incidence of diabetes has increased every decade, correlating with changes in the standard of living. Approximately 2 per cent of the Western industrialized population develop type I DM.⁴⁶ About a third of hospitalized patients on a medical service are diabetic, indicating that an enormous health care system burden is associated with the disease.⁶²

Decreased to absent insulin secretion secondary to destruction of beta cells in the pancreatic islets characterizes type I DM, formerly called juvenile onset diabetes. Decreased insulin sensitivity, that is, the number and affinity of the receptors, is the hallmark of type II DM, previously known as adult onset diabetes. Table 1 summarizes the differences between type I and II DM.¹¹⁴

Table 1. *Comparison of Type I and Type II Diabetes Mellitus*

	TYPE I	TYPE II
Clinical onset	Abrupt, symptoms severe	Mild; incidental finding
Insulin dependence	Virtually always	Rare (except after many years of diabetes)
Pathology	Insulinitis, mononuclear cell infiltration in early onset cases; eventual virtually complete destruction of β cells	Hypertrophy in early stages; atrophy and hyaline degeneration later on
Immunity		
Islet-cell antibodies	Present	Absent
Cell-surface antibodies	Present	Absent
Cell-mediated immunity	Present	Absent
Genetics	Familial aggregation HLA-associated	Strong familial aggregation; no HLA association
Other autoimmune diseases present (or in close relatives)	Frequent, particularly in older onset cases	Absent
Possible initiating events	Virus infection (? chemical toxins)	Overnutrition and obesity

From Peterson CM, Jovanovic L: What is diabetes: Types, definitions, epidemiology, diagnosis. In Friedman EA, Peterson CM (eds): *Diabetic Nephropathy, Strategy for Therapy*. Boston, Martinus Nijhoff, 1986; with permission.)

Insulin is the most powerful anabolic hormone in the body. The beta cells in the islets of Langerhans synthesize insulin and C-peptide from proinsulin within the Golgi apparatus. Insulin, not being bound to plasma proteins, is cleared 50 to 70 per cent on first pass by the liver resulting in a half-life of 5 minutes. C-peptide is eliminated by the kidney, has a half-life of 40 minutes, and is therefore a better monitor of beta-cell function than serum insulin concentration.⁴⁶

Insulin deficiency, whether relative or absolute, results in decreased cellular uptake of glucose. Consequently, the plasma glucose concentration increases. In addition, insulin deficiency causes gluconeogenesis within the liver. Glycosuria ensues when the plasma glucose concentration exceeds the renal threshold. Increased free fatty acid levels in plasma result from suppressed inhibition of lipolysis and reesterification of fatty acids, forming ketone bodies.

The clinical symptoms of acute onset include thirst, polyuria, weight loss, hunger, and fatigue. In contrast to patients with type II DM, most are underweight. One may note visual disturbances, metabolic neuropathy, and an acetone smell on the breath. Hyperosmolarity and severe acidosis (pH below 7.0) cause dehydration, hypotension, and tachycardia, followed by Kussmaul's respirations and unconsciousness. The total body potassium markedly decreases; yet serum concentrations may not indicate the extent of depletion. Therefore, acute treatment includes potassium infusion as well as fluids and insulin.

The exact etiology of type I DM remains unknown. A genetic predisposition plays a role. The HLA antigens DR3 and DR4 of the sixth chromosome are present in 95 per cent of patients with type I DM but only 50 per cent of the nondiabetic population. In addition to the genetic factors, environmental conditions are involved, since fewer than half of identical twins both develop the disease. Viruses, Coxsacki viruses in particular, and chemical compounds such as nitrosamines have been implicated as environmental factors in its development.¹²

Although the evidence is largely circumstantial, type I DM appears also to have an autoimmune etiology because type I diabetics develop other autoimmune diseases more frequently than the general population. At least 60 per cent of patients have circulating islet cell antibodies (ICAs) at the onset of symptoms. The ICAs appear for an unknown time prior to the clinical presentation of type I DM. In one study of identical triplets and twins, ICAs were present 8 years before the onset of diabetes in the sibling.¹³⁸

Ease of blood sugar control characterizes the early "honeymoon" phase of type I DM. Temporary insulin-free remission occurs in some patients. Various attempts at immunosuppression during this phase with steroids, interferon, azathioprine, antilymphocyte globulin, and plasmapheresis have been unsuccessful. These interventions were possibly attempted too late when insufficient numbers of beta cells were left to salvage. When symptoms appear acutely, fewer than 10 per cent of beta cells remain functional.¹² However, cyclosporine may

be beneficial when given to patients within the first 6 weeks of onset of type I DM. Insulin independence occurs in many such cases while C peptide concentrations increase to normal and ICA levels decrease. Patients rarely respond to cyclosporine when instituted more than 6 weeks after the onset of clinical symptoms, and diabetes always recurs when cyclosporine is discontinued.^{6, 53} In the future, by monitoring ICA concentrations in close relatives of patients with type I DM as well as in people with a high genetic predisposition, the early administration of immunosuppressive drugs may prevent the full spectrum of the disease. Meanwhile, less toxic immunosuppressive drugs are needed.

COMPLICATIONS OF TYPE I DIABETES MELLITUS

Prior to the discovery of insulin by Banting and Best in 1921, 65 per cent of type I DM patients succumbed of ketotic coma at the time of diagnosis. More recently, however, ketoacidosis occurs in about 20 per cent of newly diagnosed cases and currently accounts for only 4 per cent of the causes of death in these patients.

Yet type I DM continues to carry very high morbidity and mortality rates. The life expectancy of type I DM patients is half that of the general population,⁷⁶ and diabetics have tenfold greater mortality at any age.⁹⁴ The National Commission on Diabetes reported to the Congress of the United States that "there is widespread resignation about the inadequacy of present treatment; even with the best of medical care, the complications of diabetes still develop."⁷¹ Diabetes affects multiple organ systems. In one series, hypertension occurred in 93 per cent of patients, myocardial disorders in 80 per cent, retinopathy in 83 per cent, peripheral vascular disease in 66 per cent, and neuropathy in 55 per cent.⁹⁹

Although the microangiopathic complications of diabetes develop in almost all diabetic patients, only half become symptomatic. At the time of diagnosis, it is not yet possible to determine which half will become symptomatic from the complications. Since strict control of blood sugar slows the progression of microvascular changes, substantial efforts are made to maintain euglycemia.⁷⁸ Patients who neglect their metabolic control have higher incidences of blindness, amputations, and uremia as well as lower life expectancies than those who are better motivated.⁴⁶

Genetics may play some causative role in the complications of diabetes.⁸ However, cross-linking of collagen and other macromolecules produces many of the changes associated with the premature aging that characterizes type I DM. Glycosylation forms abnormally cross-linked collagen, enlarging capillary basement membranes and resulting in diabetic macroangiopathy. The excessive thickness depends on the duration of diabetes and the patient's age.⁸⁸

Long-lasting hyperglycemia leads to nonenzymatic glycosylation of polypeptides and proteins. Levels of glycosylated hemoglobin (A1c)

reflect the mean blood glucose concentration during the preceding 6 to 8 weeks. It normally comprises 4 to 6 per cent of the total hemoglobin concentration. Values above 10 per cent indicate DM. Despite multiple daily injections of insulin, hemoglobin A1c rarely falls below 7.5 per cent. As the complications of type I DM are at least in part caused by nonenzymatic glycosylation, hemoglobin A1c concentrations signify the control of diabetes as well as the likelihood of adverse side effects.

Patients with near normal serum glucose levels feel better than those with wide fluctuations.⁶³ Mental depression scores correlate directly with hemoglobin A1c levels. Depression arises in 38 per cent of patients with type I diabetes; major depressive episodes recur approximately once a year. Anxiety and other psychiatric disorders also surface more frequently in poorly controlled diabetics.⁹⁷ Marital problems, compounded by sexual dysfunction, develop in more than 50 per cent of men and women. The development of diabetic complications combined with failures of therapy (for example, blindness, amputation, and transplant rejection) commonly precedes recurrent depression. Active or passive suicide accounts for the 15 per cent mortality rate seen in depressed diabetics. Of those undergoing renal transplantation, 13 per cent become suicidal at some point. Patients refusing further therapy for renal failure often have profound visual impairment, resulting in loss of independence and self esteem. In some diabetics with a failed renal graft, the demands of dialysis make life intolerable. In addition, drug abuse and alcoholism frequently ensue.⁴⁷

Cardiovascular Disease

Coronary artery disease occurs early with high mortality rates, especially in those with diabetic nephropathy (DN). One-, 2- and 5-year survival rates of patients with type I DM and ESRD are 76, 45, and 19 per cent, respectively.⁸⁶ Unlike the tripathy of complications of type I DM, that is, retinopathy, neuropathy, and nephropathy, the prevalence and incidence of accelerated atherogenesis appears unrelated to blood sugar control.¹¹⁷ However, platelets and white cells¹¹⁵ hyperaggregate during hyperglycemia, contributing to vascular occlusion. Braun and coworkers²¹ demonstrated greater than 70 per cent occlusion of one or more coronary arteries in approximately a fourth of diabetic uremic patients, whereas left ventricular dysfunction occurred in 14 per cent. Fewer than 25 per cent of these patients experienced angina. Other investigators note substantial coronary occlusion (50 per cent) in approximately half of patients with type I DM and ESRD.^{14, 159} Although a poor survival rate exists for diabetics with significant coronary artery disease, those with ESRD appear to have better survival after a renal transplant than those treated with dialysis.²² However, outcome studies have been inconclusive owing to lack of good controls and the presence of other variables. Nonetheless, successful renal transplantation reverses impaired left ventricular

function in diabetic uremics. These patients, therefore, should not be excluded from renal transplantation.⁹³

The fact that most perioperative morbidity and mortality (in type I diabetics having a renal transplant) results from cardiac complications confirms the need for a thorough cardiac evaluation preoperatively.^{79, 116} This is especially so because the incidence of cardiac complications correlates with the extent of cardiac pathology, noted by coronary arteriograms.¹¹⁶ It is well known that chest pain may not occur in diabetics with severe coronary artery disease; ECG findings may not be substantial. Graded exercise testing (GXT) noninvasively assesses cardiac function. Unfortunately, many diabetic uremic patients are unable to perform exercise stress testing because of their neuropathy, retinopathy, poor physical status, or peripheral vascular disease. Only 20 per cent of type I DM patients can achieve 85 per cent of maximal heart rate for their age. Exercise-induced defects in myocardial perfusion detected by thallium strongly predict the risk of future cardiac sequelae in patients suspected of having coronary artery disease.⁸⁹ Despite low peak heart rate and low exercise level obtained, thallium stress scintigraphy accurately detects the presence of coronary artery disease in type I DM patients but poorly demonstrates the extent of involvement.¹⁰⁹ When used to assess diabetics prior to renal transplantation, the method is no more predictive of future cardiovascular events than is the history or an abnormal ECG.¹⁰⁴ Dipyridamole, a coronary vasodilator, maximizes regional differences in myocardial perfusion during thallium scanning, obviating the need for exercise. A study by Boucher and colleagues¹⁹ shows that dipyridamole thallium imaging accurately predicts subsequent cardiac events, at least in those undergoing peripheral vascular surgery.

All prospective patients for pancreatic transplantation at our institution have a GXT. If unable to perform the test or if the results are equivocal, they receive a thallium-dipyridamole scan. Cardiac catheterization is performed following an abnormal GXT or an equivocal or abnormal thallium-dipyridamole scan. If catheterization reveals significant coronary artery disease, the patient has bypass surgery prior to becoming a candidate for pancreatic transplantation.

Cardiomyopathy, another important cardiac complication of type I DM, results from thickened basement membranes and increased connective tissue in the myocardium. The work capacity of the heart decreases while work demands increase secondary to anemia and other problems associated with renal failure.⁴⁶ Echocardiography assesses myocardial function and ejection fraction; we utilize it in most subjects considered for pancreatic transplantation.

The presence of peripheral vascular disease significantly impairs renal graft survival and increases mortality in people with severe DM.¹²³ Cerebral vascular disease and stroke also contribute significantly to morbidity and mortality rates in diabetics undergoing renal transplantation.³ Furthermore, peripheral vascular disease accounts for a significant amount of morbidity in diabetic uremics. Am-

putation rates are high especially after renal transplantation and immunosuppression. Vascular access remains difficult to obtain and maintain in type I DM patients because of their accelerated atherogenesis.^{131, 132}

Neuropathy

Diabetic polyneuropathy involves actual loss of nerve fibers. Seventy per cent of patients have a mixed sensory, motor, and autonomic neuropathy while approximately 30 per cent have primarily sensory dysfunction. Predominately motor and predominately autonomic neuropathy account for less than 1 per cent of all cases.²⁶

Although present in nearly all type I DM patients, diabetic neuropathy becomes symptomatic in only half, totaling about one million Americans. Autonomic neuropathy manifests as postural hypotension, decreased sweating, diarrhea, gastric symptoms, impotence, and bladder problems, as well as failure to recognize hypoglycemia. Cutaneous sensation decreases in a stocking and glove distribution. Lower extremity motor nerve conduction velocities decrease as do sensory potential amplitudes. Tests of thermal sensation provide the most sensitive evaluation for the presence of diabetic neuropathy, which appears to first involve the smaller nerve fibers.⁷⁷

Patients with poor control of their diabetes have worse neuropathy than those with good control.¹¹⁷ Relative euglycemia may reverse some of the neurologic abnormalities including pain and decreased sensation. However, there is no evidence that tight control is better than good conventional management.¹³⁰

The thickened basement membranes of the endoneural capillaries lead to occlusive vascular changes and nerve infarctions. Nerves from patients with type I DM contain a decreased concentration of myo-inositol, impairing nerve ATPase and axonal function. Dietary supplementation with myo-inositol yields some improvements in neurologic function in experimental diabetes. Sorbitol and fructose concentrations become elevated in various tissues of type I DM patients as a consequence of glucose conversion to sorbitol by aldose reductase. Initial clinical trials for the treatment of diabetic neuropathy with aldose reductase inhibitors have produced conflicting results but are sufficiently encouraging. Larger, better controlled trials are underway.²⁶

Aspirin and other nonsteroidal anti-inflammatory drugs provide symptomatic relief for many patients with painful diabetic neuropathy. For those with persistent pain despite simple analgesics, tricyclic antidepressants usually prove effective. Type I DM patients without evidence of depression respond as well to tricyclics as those with depression.^{20, 98}

Occurring in concert with peripheral vascular disease and microangiopathy, cutaneous ulceration is an important consequence of diabetic neuropathy, which may in turn produce osteomyelitis, sepsis, and amputation. More hospital beds are occupied by diabetics with foot problems than all the other complications of diabetes put together.

Both mortality rates and economic costs for these patients are enormous.⁵⁵ Meticulous foot care is essential. Patients with diminished sensation should check their hands and feet twice a day for any breaks in skin surface. Early conscientious treatment is imperative.²⁶ Ulcerations of extremities require intensive therapy prior to pancreatic or renal transplantation.

Cardiac Autonomic Neuropathy. Sudden death in the operating room as well as the recovery room can result from diabetic cardiac autonomic neuropathy.^{38, 111} The cardiac denervation of diabetes compares to that following cardiac transplantation. Both are characterized by resting tachycardia and a fixed heart rate with loss of nocturnal slowing. Of importance is the fact that the response to atropine may be absent, and catecholamine responsiveness may also be decreased.⁵⁷ The severity of the syndrome varies as patients range from being asymptomatic to severely disabled. Symptomatic individuals have very high mortality rates, that is, 44 per cent die within 2 years, frequently from a "sudden death." Although some evidence demonstrates that tight glycemia control and that aldose reductase inhibitors may be beneficial, most patients deteriorate with time.⁵⁸

Five simple, noninvasive cardiovascular tests provide an excellent assessment of the severity of cardiac autonomic neuropathy. The heart rate response to the Valsalva maneuver, deep breathing, and standing up become abnormal in 40 per cent of patients with diabetes. The blood pressure response to standing up and sustained hand grip is abnormal in less than 20 per cent. Blood pressure abnormalities do not occur without abnormal heart rate tests, reflecting that parasympathetic involvement appears earlier than sympathetic.⁵⁶ Heart rate variation on deep breathing proves to be the most sensitive test.⁵⁸

Postural hypotension, that is, greater than a 30 mm Hg fall, decrease in blood pressure upon standing, and its associated symptoms of weakness, fainting, visual impairment, and syncope mimic hypoglycemia. The failure to increase systemic vascular resistance upon standing occurs in splanchnic as well as in subcutaneous sympathetic nerves. Many diabetics develop postural hypotension while on hemodialysis; some so severe that they cannot tolerate the procedure. Autonomic vascular neuropathy impairs the normal response to blood volume changes.¹³² Similar situations can take place during surgery and anesthesia. Patients with diabetic foot ulcers nearly invariably have autonomic neuropathy,⁷⁷ warranting anticipatory care of the potential consequences of diabetic autonomic neuropathy by the anesthesia team.

Diabetic Gastroparesis. Whereas the autonomic neuropathy of type I DM involves the entire gastrointestinal tract, its effects on the stomach assume particular importance for the anesthesiologist. Gastroparesis presents as one of the earliest complications of diabetes, producing changes similar to surgical vagotomy, that is, decreased tone of the cardiac sphincter, gastric dilation, increased fasting residue, decreased or absent peristalsis, a patulous pylorus, and an atonic duodenal bulb. Liquid emptying may be normal whereas solids are

markedly delayed. Blood glucose levels may be difficult to control as carbohydrates are absorbed more slowly with unexplained episodes of hypoglycemia ensuing from delayed gastric emptying.⁵⁷

Many patients remain asymptomatic despite demonstration of significant gastroparesis by radiograph. Although retrospective reviews show a low incidence of gastrointestinal problems in patients with type I DM, 76 per cent describe chronic gastrointestinal symptoms when specifically asked. The most common symptoms of gastroparesis are nausea and vomiting; others include early satiety, bloating, and abdominal pain. Weight loss may ensue.⁵⁹

Metoclopramide frequently alleviates the symptoms of gastroparesis via the following mechanisms: smooth muscle stimulation and increased gastric motility, inhibition of dopamine receptors for vomiting in the central chemoreceptor zone, and increased cardiac sphincter tone. Metoclopramide may be required parenterally in patients with severe gastric stasis.^{59, 133} In addition, some patients with diabetic cystoparesis benefit from metoclopramide, potentially decreasing the incidence of recurrent urinary tract infections and septicemia that result from a neurogenic bladder.¹⁵⁵ Side effects of metoclopramide, ranging from nervousness to severe extrapyramidal symptoms, occur in about 10 per cent of patients. Metoclopramide also increases prolactin levels, causing galactorrhea in occasional patients.

Retinopathy

Retinopathy infrequently occurs at the time of diagnosis of type I DM. Microaneurysms appear about 5 to 10 years after onset of the disease and are then followed by hemorrhages and exudates. After 15 to 20 years, retinopathy affects nearly all patients, with significant visual impairment occurring in one third. Whether retinopathy can be prevented by maintenance of euglycemia is undergoing clinical investigation.⁵²

Diabetic retinopathy presents as a spectrum classified as background, preproliferative, and proliferative phases. Intraretinal, mainly exudative changes characterize background retinopathy. Preproliferative retinopathy is associated with ischemic changes, and patients must be carefully watched as they are at high risk for developing proliferative retinopathy. If not treated within 2 years, 25 to 40 per cent of patients with proliferative retinopathy suffer severe visual loss.⁸³ Growth hormone levels are higher in patients who develop retinopathy, perhaps helping to identify high-risk patients at an early stage.¹¹⁹ Near normal blood sugar levels slow the progression of retinopathy.¹⁵⁸ Effective antihypertensive therapy and improved dialysis techniques, as well as laser therapy and microsurgery, further help to maintain vision.

Renal transplantation stabilizes retinopathy in some patients, but it progresses in others.⁶⁹

Stiff Joint Syndrome

The proliferation of connective tissue, frequently occurring in type I DM, predisposes to joint problems, including Dupuytren's con-

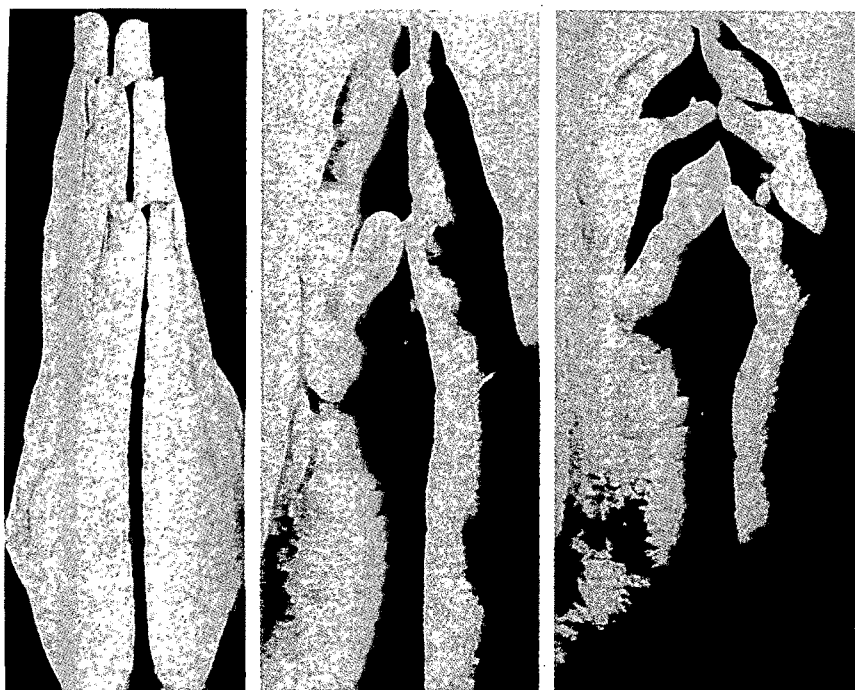


Figure 2. Diabetic stiff joint syndrome increasing in severity. The patient on the right had severe limitation with inability to approximate the palmar surfaces of finger joints. (From Rosenbloom AL: Skeletal and joint manifestations of childhood diabetes. *Pediatr Clin North Am* 31:569, 1984; with permission.)

tracture, flexor tenosynovitis (trigger finger), reflex sympathetic dystrophy, carpal tunnel syndrome, stiff hand syndrome secondary to vascular insufficiency, and diabetic stiff joint syndrome (DSJS). In diabetics Dupuytren's contractures develop predominantly in the third and fourth fingers rather than in the usually involved fourth and fifth digits. Reflex sympathetic dystrophy presents bilaterally in 42 per cent of patients with diabetes in contrast to only 5 per cent of nondiabetics. Diabetes is the most common disorder associated with carpal tunnel syndrome.¹²⁴

The stiff joint syndrome transpires in 30 to 40 per cent of severe diabetics and is often accompanied by nonfamiliar short stature and tight waxy skin. Changes begin in the metacarpophalangeal and proximal interphalangeal (PIP) joints of the little finger and spread medially (Fig. 2). These perturbations may be preceded by increased thickness of the skin although the gross appearance looks normal.¹²⁹ The joint changes are independent of age, sex, and age at onset of diabetes but do correlates with the duration of diabetes.⁷⁰ Campbell et al³² report greater decrements in joint mobility in patients with poor

glycemic control. Another series¹²⁹ notes decreased skin thickness after 3 months of euglycemia.

Skin and joint changes result from increased collagen deposition, suggesting that the term "diabetic collagenosis" is more descriptive. Whether the increased collagen is related to increased synthesis, decreased degradation, or both remains to be determined. Diabetic fibroblasts generate more collagen *in vitro* than normal. This collagen is 50 per cent less soluble in acetic acid than normal, indicating resistance to degradation, and it has increased cross-linkage. Nonenzymatic glycosylation of collagen from diabetic patients with skin changes is 13 times that of normal controls.²⁹ Resulting from tissue accumulation of sorbitol, increased hydration of collagen produces the rigid joints and the other manifestations of DSJS.²⁹ Animal studies¹⁶² indicate that prostaglandin metabolism also plays a role in the abnormal collagen deposition. Experimental use of sorbinil⁵⁴ and cyclooxygenase inhibitors¹⁶² improve joint motion and strength.

Pulmonary Changes

Abnormal pulmonary function develops in many type I DM patients. Clinical symptoms may be absent although the vital capacity falls 2 standard deviations below normal.³⁰ Closing capacity to total lung capacity ratios are significantly higher in diabetics than in controls. Elastic recoil and diffusing capacity become abnormal. Pulmonary capillary blood volume decreases.¹²⁷ All of these changes indicate premature aging of the lungs.

Nephropathy

When type I DM develops before age 20, renal disease subsequently becomes a leading cause of death.¹¹⁹ In fact, diabetes produces 25 per cent of chronic renal failure cases and increasingly accounts for renal replacement (dialysis or transplantation). The mortality rate is three times that of patients with other etiologies of ESRD,^{35, 131, 157} while survival rates are much lower than in diabetics without ESRD. Although nearly all individuals with type I DM have glomerular changes, clinical diabetic nephropathy (DN) develops in about half, generally presenting 10 to 20 years following diagnosis. After 35 years of disease, only 4 per cent of patients subsequently develop proteinuria.⁵ Nephropathy occurs more frequently in men,^{5, 45} smokers, blacks,¹²⁵ and those with higher insulin requirements. Although the cause of DN is not completely understood, elevated levels of activated T-lymphocytes during the onset of proteinuria suggests an immune mechanism.^{2, 140} Glycosylation of the glomerular basement membrane may confer antigenicity.

Clinical DN is defined as proteinuria, which is detectable by the urine dipstick test or greater than 0.5 g per 24 hours in at least four consecutive 24-hour urine specimens. Microscopic proteinuria precedes clinical proteinuria by as long as 10 years (Table 2).³⁵ The degree of microalbuminuria strongly correlates with subsequent development of clinical nephropathy and ESRD. Conversely, the absence

Table 2. *Classification of Diabetic Nephropathy*

STAGE	TIME SINCE ONSET (YR)	CHARACTERISTICS
1	0	Renal hypertrophy, hyperfiltration, normal GBM thickness, high basal albuminuria, corrected by insulin therapy
2*	1-10	Thickening of the GBM, increased mesangial matrix, hyperfiltration, increased albuminuria after exercise or when diabetes is suboptimally controlled
3 (incipient DN)	1-15	In 30-40% of the patients microalbuminuria (30-300 mg/day or 20-200 μ g per min) and microhypertension; risk factors: microalbuminuria >50 mg per day, GFR > 150 ml per min per 1.73 m ²
4 (overt DN)	10-20	In 30-40% of the patients diffuse or nodular glomerulosclerosis, macroproteinuria (>500 mg per day), frequent hypertension, possible development of nephrotic syndrome, gradual lowering of GFR (mean 1.2 ml per min month)
5 (uremia)	20-30	Glomerular sclerosis and hyalinosis, GFR < 10 per ml per min, sometimes early symptoms of uremia

* This stage appears at present still incompletely defined and of unknown prognostic significance.

From Castiglioni A, Savazzi GM: Physiopathology and clinical aspects of diabetic nephropathy. *Nephron* 50:151, 1988; with permission.

of microalbuminuria usually rules out the occurrence of DN within 10 to 15 years. Patients with microscopic proteinuria have potentially reversible lesions and, therefore, should be aggressively treated with strict metabolic control. Once significant proteinuria occurs, however, diabetic patients follow a relentless downhill course to ESRD despite intensive medical therapy, indicating a self-perpetuating process.¹⁵⁶ Additionally, a decline in glomerular filtration rate (GFR) may occur in patients without persistent proteinuria and with good blood sugar control. Indeed, etiologies other than diabetes can be responsible for ESRD, and they should be considered in patients without other severe, diabetic sequelae (that is, retinopathy or neuropathy).⁶⁹ Proliferative retinopathy leads to blindness more quickly in patients with DN than in those without.⁴⁵

Autoregulation—the maintenance of a fairly constant GFR with changes in blood pressure over 80 mm Hg—occurs in normal, de-

nervated, and isolated kidneys. In some patients type I DM induces a loss of autoregulation wherein $\Delta \text{MAP}\% = \Delta \text{GFR}\%$. The afferent arteriole usually becomes hyalinized in type I diabetes; this effect could impair vascular responses to pressure changes.¹¹³ Autoregulation of cerebral, skeletal muscle, and subcutaneous tissue also becomes disturbed. The microcirculation's loss of self regulation permits transmission of systemic pressures to the glomerulus with adverse effects.³⁵ Thus, vigorous control of hypertension is mandatory in the preclinical phase of DN. Each year of effective antihypertensive therapy preserves as much as 9 ml per min of creatinine clearance.^{101, 112} Angiotensin-converting enzyme inhibitors are particularly efficacious in reducing proteinuria in overt DN.¹⁶ Additionally, antihypertensive therapy slows the progression of retinopathy.⁶¹

Renal replacement therapy in type I DM patients with overt nephropathy eventually becomes necessary. Initially, there was little enthusiasm for renal transplantation in type I DM patients as it was feared the diabetic changes would recur in the new kidney. Frequently, chronic dialysis was withheld as well because of the poor prognosis of these patients.⁸⁵ However, encouraging results were subsequently observed in severe diabetics who underwent renal transplantation.⁴ Microscopic changes develop in the transplanted kidney, but only half of the grafts appear to slowly develop functional impairments, with increased serum creatinine levels.⁹⁶ At present, no single criterion makes a patient with ESRD secondary to type I DM unsuitable for renal transplantation. An estimated 4000 patients worldwide with type I DM have undergone renal transplantation since 1970. Graft survival has improved, equaling that of the nondiabetic patient.⁶⁵ For the severe diabetic, the advantages of renal transplantation over dialysis have become quite clear. The availability of money, donor organs, and technical resources constitute the greatest restrictions. Of note is the fact that diabetics who receive living related donor (LRD) transplants survive longer than cadaver kidney recipients. Also, poor outcome follows a second renal transplant.¹⁰⁸

INDICATIONS FOR PANCREATIC TRANSPLANTATION

Unlike liver or heart transplantation, pancreas transplantation is not an emergent life-saving procedure. "No one in the industrialized world today dies from acute lack of insulin."¹⁴² Except for the rare patient with life-threatening, extremely labile diabetes, the provision of an insulin-independent life per se does not justify the inherent hazards of long-term immunosuppression. Thus, only a small group of diabetics are excellent candidates for isolated pancreas transplants. These patients have extremely brittle diabetes and experience multiple episodes of ketoacidosis despite well-documented attempts at tight glucose control. They may otherwise be well with few vascular

complications but should be incapacitated by the disease. A pancreas transplant can reverse labile diabetes and provide a normal lifestyle, free from the risk of recurrent ketoacidosis.

In type I diabetics, who have not developed significant complications, the risks of immunosuppression may exceed those of remaining diabetic. However, the complications of diabetes, especially nephropathy, become devastating in half of type I DM patients. Currently, most transplant surgeons perform pancreatic transplants only as a combined procedure with renal transplantation. These patients are already subject to the risks of immunosuppression. Transplanted kidneys usually demonstrate rejection earlier than pancreatic grafts, so that antirejection therapy often begins prior to signs of pancreatic rejection.²⁴

The addition of a pancreatic graft does not appear to significantly affect either patient or graft survival following renal transplantation.^{25, 144} Furthermore, the addition of a pancreatic graft to a renal graft offers a life that may be both dialysis and insulin free. The quality of life improves markedly and patients need only manage immunosuppression instead of immunosuppression and diabetes.^{23, 105} Simultaneous pancreas and renal transplantation from the same donor results in a greater success rate.²³ Therefore, combined pancreatic-renal transplantation should be considered in all type I DM uremic patients for whom a suitable LRD is not available for renal transplantation.

Patients with elevated growth hormone levels, increased renin concentrations, and stiff joints appear to be at greatest risk for developing the complications of type I DM. Increased renin levels correlate with poor blood sugar control and appear to be a good marker for those who will develop severe diabetic complications.⁹⁵ Whether patients with such findings will benefit from early, preuremic pancreatic transplantation remains to be seen. On the one hand, pancreatic transplantation alone (PTA) prior to uremia reverses the morphologic manifestations of nephropathy and the relentless progression to ESRD. Early nephropathy may thus become a more widespread indication for pancreatic transplantation. On the other hand, the transplant team must accurately determine the patient's renal function. In those with renal compromise, further deterioration of renal status may occur following pancreatic transplantation and subsequently require a renal transplant.¹⁴⁵ The situation is complicated by the need for immunosuppression with cyclosporine, which can produce additional impairment of renal function. When renal biopsy shows that the mesangium comprises greater than 40 per cent of glomerular volume, nephropathy is considered too advanced for pancreatic transplantation alone, regardless of other parameters.¹⁴⁴

As less toxic and more effective immunosuppressive regimens become available, pancreas transplantation should be applicable to a wider range of diabetic patients. Prior to the onset of late, frequently irreversible complications, pancreatic transplantation would then be a mode of prevention rather than treatment.⁹²

SURGICAL ASPECTS OF PANCREATIC TRANSPLANTATION

During the first decade of pancreatic transplantation, technical failures and complications accounted for many graft failures. Problems primarily related to (1) inadequate control of exocrine secretions from the pancreas and (2) surgical complications including pancreatitis, pancreatic ascites, pseudocysts, fistulas, anastomotic leaks, and wound complications.⁷² Multiple surgical approaches have been attempted for pancreatic transplantation and several continue to be used. Most differences relate to the handling of exocrine secretions (Table 3). In the first two clinical pancreatic transplants, Kelly and coworkers⁸⁵ utilized the body and tail segment with ligation of the pancreatic duct. Obstruction of the duct produced severe pancreatitis with destruction of endocrine as well as exocrine function. Their second attempt utilized the entire duodenum and first part of the jejunum, which they exteriorized similar to an ileostomy. Because of poor outcomes, initial work in the procedure generated little interest until the advent of pancreatic duct occlusion with various polymers. Duct occlusion by injection currently carries the lowest early technical failure rate. In essence, occlusion with polymers postoperatively¹⁰ causes involution of exocrine glands. However, duct-filling methods sometimes cause fibrosis of the entire graft, including the islets of Langerhans.

Most surgeons now use either bladder or enteric drainage of exocrine secretions. Although enteric drainage is the most physiologic approach, fistulas frequently develop and heal poorly at best. Also, abscesses, intestinal obstruction, and enteric contamination of the graft are not uncommon.⁸⁰ As suggested by Groth and Tyden,⁷³ exteriorizing the exocrine drainage with a catheter for several weeks, until the wound heals markedly, decreases the number of postoperative fistulas and other complications.

The majority of surgical techniques utilize segmental grafts because of the ease of harvesting and implantation and because they

Table 3. Pros and Cons Regarding the Three Most Widely Used Methods for Handling the Exocrine Secretion

	TECHNICAL ADVANTAGE	TECHNICAL DISADVANTAGE	MONITORING OF EXOCRINE SECRETION
Ductal filling	Simple	Risk for fibrosis and atrophy	Requires initial exteriorization by ductal catheter and delayed filling
Enteric drainage	Physiological	Risk for enteric contamination	Requires initial exteriorization by ductal catheter
Urinary tract drainage	Usually sterile environment	Nonphysiologic, bicarbonate depletion	Readily available by urinary assays

allow the simultaneous harvesting of the liver.⁷³ Segmental transplantation is necessary as well during use of LRD kidneys. The main drawback with segmental grafts is a high incidence of vascular thrombosis.¹²¹

In 1982, Starzl's group re-examined the method of whole pancreas grafting.¹³⁹ At the same time, canine studies demonstrated a low incidence of complications when the exocrine secretions were drained into the urinary bladder.¹³⁵ Pancreatic enzymes are not activated by substances in urine as they are by intestinal contents. Therefore, the incidence of fistula formation has been less with bladder drainage. An additional advantage is that rejection may be detected by a decrease in urinary amylase concentration. Over 90 per cent of the pancreas has undergone damage when glucose intolerance appears. Thus, pancreaticocystostomy solved two of the primary reasons for graft failure in the past, namely difficult surgical technique and delayed recognition of rejection. And, bladder drainage has become the technique of choice for most American surgeons, especially because graft survival rates are higher with this method (90 per cent) compared with enteric drainage (70 per cent). When combined with a LRD-renal transplant, pancreatic transplantation with enteric drainage yields similar results to bladder drainage, with fewer sequelae.¹²⁰

Electrolyte abnormalities may arise as a result of bladder drainage as significant amounts of bicarbonate are lost through the urine. This is, however, relatively easily solved by the administration of either oral or intravenous bicarbonate. Hyperchloremic metabolic acidosis, resulting from inadequate bicarbonate replacement, can be severe during periods of renal dysfunction.¹⁰⁷

In our center, the surgical team transplants the whole pancreas (versus segments), utilizing bladder drainage, in combination with renal transplantation (Fig. 3). The spleen is transplanted along with the pancreatic graft to increase initial blood flow and to facilitate placement of the pancreas. At the end of the procedure, when the ureter has been anastomosed to the bladder, the donor's spleen is removed. Deierhoi and colleagues⁴⁹ have observed graft versus host disease when the spleen is left in.

Organ Preservation

Until recently pancreatic transplantation was conducted as an emergent procedure once a suitable donor was located and the organ harvested, since graft survival rates were extremely poor when organs had ischemic times longer than 6 hours. Belzer and Southard developed a solution that allows good preservation of canine pancreatic and renal grafts for 72 hours (Table 4). Rather than glucose, lactobionate is used because of its impermanence and large molecular mass. Employed in Collins' solution, glucose stimulates undesirable production of lactic acid and hydrogen ions. Raffinose, a saccharide also having a large molecular mass, enhances further osmotic support. Hydroxyethyl starch prevents expansion of the extracellular space and provides colloidal osmotic pressure. Adenosine acts as a precursor for ATP re-

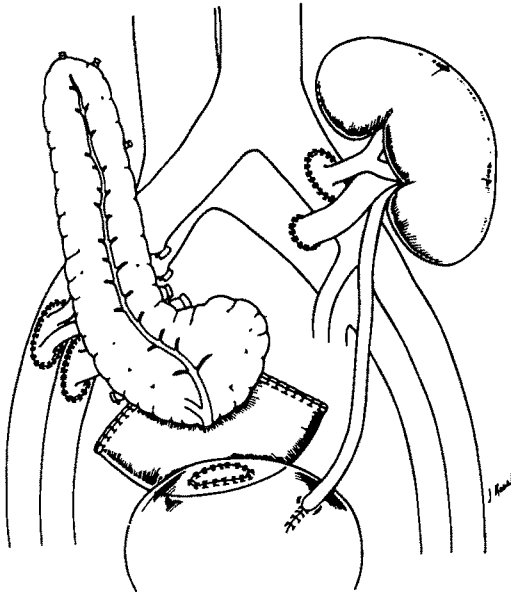


Figure 3. Combined kidney-pancreas transplantation with the duodenal segment technique. (From Sollinger HW, Stratta RJ, D'Alessandro AM, et al: Experience with simultaneous pancreas-kidney transplantation. *Ann Surg* 208:475, 1988; with permission.)

synthesis during reperfusion. Glutathione depletion occurs during ischemia; its addition to the preservation solution provides for reduction of cytotoxic agents, including hydrogen and lipid peroxides, disulfides, ascorbate, and free radicals. Allopurinol inhibits xanthine-oxidase-catalyzed generation of superoxide.¹³ D'Alessandro et al.⁴² recently reported their experience with this preservation solution in human pancreatic transplantation. The donor grafts were perfused in situ with 1000 ml of the solution, removed, and flushed with an ad-

Table 4. UW Cold Storage Solution

SUBSTANCE	AMOUNT IN 1 L
K ⁺ -lactobionate	100 mmol
KH ₂ PO ₄	25 mmol
MgSO ₄	5 mmol
Raffinose	30 mmol
Adenosine	5 mmol
Glutathione	3 mmol
Insulin	100 U
Penicillin	40 U
Dexamethasone	8 mg
Allopurinol	1 mM
Hydroxyethyl starch	50 g

From Belzer FO, Southard JH: Principles of solid-organ preservation by cold storage. *Transplantation* 45:673, 1988; with permission.

ditional 500 ml of the solution. Early graft function was excellent with ischemic times up to 19 hours, averaging 10.2 hours.

Immunosuppression

Initially, the pancreas appeared to be highly immunogenic with frequent rejection episodes. Prior to bladder drainage of exocrine secretions, recovery from rejection was extremely poor. More recently, authorities have not confirmed the high level of acute rejection for pancreatic grafts. Indeed, they believe that the pancreas may be less susceptible to acute rejection than the kidney and that many early graft failures previously attributed to rejection were actually lost by technical failures. Alternatively, rejection of the pancreas may occur at a later stage than the kidney, and the anti-rejection therapy given for the kidney may mask or prevent the pancreatic rejection. Chronic rejection occurs similarly in both pancreatic and renal grafts.¹⁴⁹

Following combined pancreatic-renal transplantation, quadruple immunosuppression with Minnesota antilymphoblast globulin (MALG), prednisone, azathioprine, and cyclosporine results in the following 1-year survival rates: pancreatic graft (84 per cent), renal graft (94 per cent), and patient survival (96 per cent).¹³⁷ The MALG is initiated on the first postoperative day and given for 10 to 14 days. The dose is adjusted to maintain the white blood cell count over 3000 per cm^3 and the platelet count greater than 50,000 per cm^3 . Cyclosporine therapy begins on the third postoperative day with the dose adjusted to achieve trough levels between 200 to 400 ng per ml. Nephrotoxicity and glucose intolerance ensue with higher doses.⁷⁵ Following renal transplantation, patients receiving cyclosporine have a higher incidence of diabetes than those receiving other immunosuppressive drugs, indicating that cyclosporine might be responsible.¹⁶⁰ Yet, low doses given after pancreatic transplantation are not toxic; patients have excellent glucose tolerance.³³

Initially, acute rejection is managed with high-dose steroids. When this fails, the monoclonal antibody OKT₃ is administered and has been shown to reverse 84 per cent of cases of refractory rejection.¹⁴⁰ Initial use of OKT₃ avoids prednisone therapy, which often produces glucose intolerance, making evaluation of ongoing pancreatic rejection difficult.

Bucin²⁸ states that preoperative blood transfusions may improve renal graft survival by modulating the immune response. At the University of Wisconsin, a pre-pancreatic transplant requirement is a minimum of five random blood transfusions.¹³⁷ Although cyclosporine attenuates some of the increased survival induced by blood administration, the "transfusion effect" remains significant particularly in black patients.³⁶

Islet Cell Transplantation

Islet cell transplantation has very rarely been successful in humans. The procurement of too few viable cells constitutes the main cause of failure. Other reasons for the poor success include increased

susceptibility or delayed recognition of rejection as well as transplantation to inappropriate sites.¹⁴⁶

Although fraught with logistic and ethical problems of supply, fetal pancreatic islet cells replicate easily in culture whereas the exocrine cells do not. Transplantation of cultured human fetal pancreas was reported in four patients with type I DM. One had good graft function.¹⁴⁸ Twelve of 300 fetal pancreatic grafts performed in China attained good function.¹⁰³ Studies utilizing tissue from aborted fetuses are presently not allowed in the United States.

ANESTHETIC MANAGEMENT

Preoperative Assessment

A century ago John Hunter wrote "an acquaintance with the constitution of the patient to be operated upon is absolutely necessary." His statement remains true and is especially applicable for type I DM patients undergoing pancreatic transplantation. As most centers are performing pancreatic transplantation only as a combined procedure with kidney grafting, most of the same considerations of anesthesia for renal transplantation are applicable.⁶⁸

Prior to coming to the operating room, patients are visited during which time a history and physical examination is completed. An understanding of the patient's emotional status, hopes, and expectations facilitates preanesthetic evaluation and alleviation of anxiety. Preoperative medications include the patient's cardiovascular drugs such as antihypertensives and particularly beta blockers, clonidine, and angiotensin-converting enzyme inhibitors. Severe withdrawal syndromes for clonidine and beta blockers mandate their continuance perioperatively.²⁷

The complications of type I DM have special implications for the anesthetic management of these patients. In particular, the presence of DSJS dictates preparation for a difficult intubation, including the availability of a fiberoptic bronchoscope or Sanders jet ventilator. An evaluation of the patient's finger joints provides evidence of DSJS. If the joints appear involved, then a thorough evaluation of the airway, especially the degree of extension at the atlanto-occipital joint becomes imperative. "Almost all of the extension of the head or the neck that is helpful to the laryngoscopist takes place at the atlanto-occipital joint and the extension that can be achieved is limited by the abutment of the atlas against posterior tubercle of the occiput."¹⁰⁶ In some diabetics with DSJS, severely limited atlanto-occipital joint makes intubation via direct laryngoscopy impossible. Nasal intubation with the fiberscope¹²⁶ or an awake blind nasal approach then becomes indicated. Ventilation with a jet ventilator (Sanders) through a cricothyrotomy cannula may be necessary until an airway can be established. Because pancreatic transplantation cannot be postponed for several days when a difficult intubation arises, preoperative assessment of the

airway is imperative with appropriate preparations made prior to induction of anesthesia.

Type I DM patients often have significant gastroparesis even in the absence of symptoms. Thus, premedication includes a H_2 antagonist as well as metoclopramide. During induction cricoid pressure is applied. Whenever possible, mask ventilation is avoided, endeavoring to prevent further gastric distention, regurgitation, and aspiration. Although transtracheal jet ventilation via cricothyrotomy may be life saving when intubation proves impossible, it also is best avoided in the presence of gastroparesis. Therefore, awake intubation should be employed, prior to induction, in patients with gastroparesis when DSJS compromises the airway. On occasion, tracheostomy by the surgical team is necessary for airway provision.

Monitors

A printout of the baseline ECG allows correlation of T wave changes with serum potassium levels intraoperatively. Other routine noninvasive monitors include pulse oximetry, capnography, temperature, and an esophageal stethoscope. In most cases, our surgeons insert a triple lumen central venous catheter on the ward preoperatively. A radiograph verifies position of the catheter and the film is brought to the operating room. Pulmonary artery catheters are usually not used because our patients have had an extensive preoperative workup to rule out significant coronary artery disease, and cardiovascular status receives necessary stabilization before surgery.

After arrival in the operating room, patients frequently receive an arterial line prior to induction of anesthesia for blood pressure monitoring, arterial gas analysis, and blood chemistry determinations. We most often use the radial artery. However, the axillary artery, which is less likely to thrombose and, therefore, less likely to interfere with future dialysis access, may be preferable. The University of Wisconsin team does not use arterial lines for their patients undergoing pancreatic transplantation. Indeed, blood chemistries and venous gases (for acid-base status) can be sampled from the multilumen CVP line.

Induction of Anesthesia

The choice of agents for induction of anesthesia must take into consideration the likelihood of both gastroparesis and peripheral neuropathy associated with type I DM patients. The need for a rapid sequence intubation must be balanced against possible hyperkalemia (secondary to succinylcholine). Furthermore, both a possible difficult intubation and gastroparesis dictate maximal relaxation in the least possible time.

A single dose of succinylcholine to patients with renal failure increases serum K^+ 0.1 to 0.2 mEq per L, similar to nonrenal failure patients. However, a second dose has been reported to cause increases greater than 1.0 mEq per L in ESRD patients.^{87, 158} If the serum potassium (K^+) is below 5.5 mEq per L, succinylcholine can usually be utilized. Hyperkalemia following a single dose of succinylcholine in

Table 5. *Conditions for Endotracheal Intubation 90 Seconds After Atracurium 0.5 mg per kg in Normal and Anephric Patients*

	NORMAL	ANEPHRIC
Number	25	26
Good	15(60%)	9(35%)
Adequate	10(40%)	17(65%)
Poor	0	0

Conditions were said to be "good" if the cords were abducted and there was no cough on intubation, and "adequate" if there was slight cough only on intubation.

From Hunter JM, Jones RS, Utting JE: Effect of acute hypocapnoea on renal function in the dog artificially ventilated with nitrous oxide, oxygen and halothane. *Br J Anaesth* 52:197, 1980; with permission.

patients with diabetic neuropathy *must* be exceedingly rare, but remains a potential cause for concern.⁶⁰

If it is decided not to use succinylcholine for rapid intubation, a large dose of vecuronium, approximately 0.2 mg per kg, is used. We prefer not to employ atracurium in this situation because it produces less adequate intubating conditions in patients with ESRD than in the normal population⁸² (Table 5), and larger doses of atracurium elicit histamine release. However, repeated doses of vecuronium have some cumulative effects in patients with ESRD.¹⁵ Therefore, we maintain neuromuscular blockade with atracurium after rapid intubation with succinylcholine or vecuronium. The pharmacokinetics of atracurium are so predictable in renal failure that it is safe to repeat doses almost regardless of neuromuscular stimulation.⁴⁴

Thiopental, midazolam, fentanyl or sufentanil, lidocaine, and other agents are given during induction according to the preference of the anesthesiologist, who considers the needs of the particular patient. An early case report suggested a prolonged duration of action of sufentanil in patients with ESRD. However, pharmacokinetic and pharmacodynamic studies of 2 µg per kg IV revealed no differences compared with patients with normal kidney function.⁶⁴ Nonetheless, renal failure profoundly affects the pharmacokinetics and pharmacodynamics of many other drugs administered in the perioperative period.⁶⁷ Thiopental should be given judiciously in patients with lower CVP values, to avoid significant hypotension. Etomidate is an alternative.

Intraoperative Management

In our center, most anesthetics for renal-pancreatic transplants are maintained with isoflurane in oxygen-air. Enflurane has been successfully used for renal transplantation in hundreds of patients.⁵⁰ Nonetheless, most anesthesiologists prefer isoflurane, whose limited metabolites do not include inorganic fluoride. Further benefits of isoflurane include less myocardial depression than either halothane or enflurane,¹¹ particularly in patients taking calcium channel block-

ers.⁸⁴ In addition, less sensitization of the myocardium to catecholamines accompanies isoflurane anesthesia. In view of the patients' extensive preoperative cardiac evaluation, concerns regarding intracoronary "steal" secondary to isoflurane assume secondary importance. Occasionally nitrous oxide may be given, particularly if there is difficulty in controlling the patient's blood pressure.

The concentrations of anesthetic agents, carbon dioxide, and oxygen are monitored in the breathing circuit. Blood-gas partition coefficients decrease secondary to the anemia accompanying renal failure, affecting uptake and distribution of inhalation agents. Renal perfusion and GFR decrease during both hypercarbia and hypocarbia.^{51, 81} Therefore, ventilation is controlled to maintain eucarbia. The anesthetic gases are humidified, filtered, and warmed. Intravenous fluids are also warmed. Low flow or closed circuit anesthesia further helps to maintain normothermia.

In many cases we supplement isoflurane with intravenous fentanyl or sufentanil as needed throughout surgery, especially in diabetics with coronary artery disease or significant hypertension. During clamping of the iliac vessels, fentanyl may be sequestered in the leg. Following revascularization serum fentanyl levels increase.⁷⁴

Blood glucose, gases, and electrolytes are monitored every 30 minutes intraoperatively, mandating quick turnaround laboratory time. Our anesthesia stat laboratory is located within the operating room suite. We attempt to maintain the serum glucose concentration at approximately 300 mg per dl prior to vascular unclamping. Following reperfusion of the pancreatic graft, serum glucose usually falls to normal levels within the first hour. A relatively prolonged ischemia time may result in a slower return to normal levels. Exceedingly high blood sugar levels may require IV insulin intraoperatively (via small increments or continuous infusion).

Sealey¹²⁸ reported that magnesium, calcium, sodium, and chloride levels generally remain normal during combined pancreas and kidney transplantation. However, serum potassium levels became abnormal in 2 of 5 patients. In one patient, a high potassium level normalized with insulin administration. The other individual had a low level that required supplementation. Good glucose homeostasis did not ensure adequate potassium balance. Therefore, it is necessary to follow concentrations of both glucose and potassium perioperatively. Administration of blood potentiates hyperkalemia. Hyperglycemia frequently follows the administration of steroids, which increase insulin requirements by approximately 50 per cent.

Fluid loading and moderately high filling and systemic pressures, that is, a central venous pressure of 12 mm Hg and systemic systolic pressure of 140 mm Hg, optimize early renal graft function.^{34, 43} We have not encountered the difficulty in achieving these filling pressures using blood, crystalloids, and albumin, that Sealey¹²⁸ reported during combined pancreas-renal transplantation. In his series, two patients who had received nifedipine preoperatively developed marked hypotension secondary to a decrease in ionized calcium fol-

lowing the administration of citrated blood and albumin. Calcium administration restored the hemodynamic parameters. Low ionized calcium in combination with hyperkalemia severely impairs cardiac function.

Optimal perioperative hydration also reduces the nephrotoxicity associated with cyclosporine.³¹ Both cyclosporine and part of its vehicle, cremophor, potentiate neuromuscular blockade, particularly that induced by vecuronium and pancuronium and less so than that produced by atracurium.^{41, 66} Although we presently do not initiate cyclosporine until the third postoperative day, such potentiation generates concern when patients undergo subsequent procedures.

To enhance renal function, mannitol 25 g and furosemide 400 mg are administered prior to vascular unclamping. Mannitol does not readily enter cells and, therefore, draws water out of the cells into the extracellular space. This shift causes an increase in serum potassium of 0.3 to 0.6 mEq per L.^{37, 102} We initiate a dopamine infusion when the renal graft does not have a good appearance or difficulty is encountered keeping the systolic blood pressure above 130 mm Hg.

Type I DM patients with cardiac autonomic neuropathy may suddenly develop bradycardia and hypotension intraoperatively for no apparent reason. Atropine may not be effective, and epinephrine is then given to restore hemodynamic stability.³⁸

At the conclusion of surgery, reversal agents (for example, neostigmine and glycopyrrolate) are administered to antagonize neuromuscular blockade. Severe bradycardia and hypertension can occur following reversal of neuromuscular blockade with this combination, especially in diabetics with cardiac autonomic neuropathy.¹⁴⁷ Again, IV epinephrine may be necessary, because atropine may not be effective. Although renal failure does not affect clearance of vecuronium or atracurium, clearance of the anticholinesterase drugs is markedly prolonged.⁴⁰ Therefore, "re-curarization" rarely becomes a problem with the use of newer relaxants in people with compromised renal function.

Early Postoperative Care

Following combined pancreatic-renal transplantation, patients are left intubated and sedated. Mechanical ventilation is maintained in the surgical intensive care unit until the patients are hemodynamically and metabolically stable and have fully recovered from anesthesia.

In diabetics with autonomic neuropathy, sudden cardiac arrest in the early postoperative period looms as a possibility. Abnormal ventilatory and circulatory responses to hypoxia have been implicated. In these patients, hypoxia produces bradycardia, hypotension, and respiratory depression instead of the usual reflex-mediated responses. Additionally, loss of cholinergic tone in the airways resulting from pulmonary autonomic neuropathy predisposes to the development of hypoxia, especially in the presence of residual anesthetics and analgesics.¹¹¹ The use of short-acting anesthetic drugs and adjuvants

should decrease the possibility of "sudden cardiac arrest." Monitoring of respiratory function both by close observation, oximetry, and arterial blood gas values must continue in the intensive care unit.

DONOR MANAGEMENT

The dissection required for pancreas procurement is far more extensive than for kidneys alone. Blood and third space losses can be significant, frequently requiring transfusion as well as massive fluid replacement. Dopamine should be kept under 10 μg per kg per min as higher doses can produce acute tubular necrosis post-transplant. Some patients receive Pitressin (vasopressin) for diabetes insipidus, which may also impair renal function.

An intra-arterial cannula facilitates hemodynamic monitoring during procurement. Donors with brain death have significant hemodynamic instability, which results from dysfunction of the vasomotor center (leading to poor ventricular function, vasodilation, and low system vascular resistance). Typically, patients have received fluid restriction and diuretic therapy for a neurologic catastrophe. This accentuates the development of profound hypotension.

The anesthesia team continues mechanical ventilation in the operating room until the aorta is clamped and in situ perfusion with preservation solution begins. Pancuronium facilitates surgical exposure and prevents patient movement. Occurring in brain-dead patients, the Lazarus' sign consists of arm motion, shivering, and gooseflesh after discontinuation of mechanical ventilation. Despite complete brain death, the pulse and blood pressure may increase with surgical incision. The anesthesia team attempts to maintain the rule of 100's criteria (systolic pressure > 100 mm Hg, urine output > 100 ml per hr) and may be requested to administer heparin and chlorpromazine prior to aortic clamping.¹⁵⁴

RESULTS OF PANCREATIC TRANSPLANTATION

All patients with functioning pancreatic grafts become insulin independent, possess normal hemoglobin Alc values, and have normal fasting and postprandial blood glucose levels. However, the glucose tolerance test may remain somewhat abnormal, probably due to the effects of steroids and cyclosporine. Several studies^{1, 9} indicate that pancreatic-kidney transplants decrease morbidity by lessening, stabilizing, or reversing retinopathy, neuropathy, and the vascular changes. Bohman and coworkers¹⁷ note that a successful pancreatic graft prevents recurrence of nephropathy in the transplanted kidney. An unbiased analysis of the effect of pancreatic transplants alone on native kidneys is complicated by the nephrotoxic properties of cyclosporine. In most cases, creatinine clearance initially decreases but then stabilizes.⁴⁸

The beneficial effects of pancreatic transplantation on diabetic neuropathy^{110, 141} may result in part from the coexisting renal graft. That is, a kidney placed during the combined transplant procedure may improve nerve function (for example, increased conduction velocity) by alleviating the neurologic effects of uremia. However, renal transplantation alone usually does not improve signs and symptoms of diabetic neuropathy, which often worsens progressively.^{69, 153} Additionally, some neurologic improvement occurs after pancreatic transplant alone in nonuremic individuals.¹⁴⁵ Solders and associates¹³⁴ do not find reversal of cardiac autonomic neuropathy following successful pancreatic transplants.

Fear of blindness is the overwhelming reason stated by patients desiring pancreatic transplantation.⁷ However, contradictory findings regarding the effects of combined transplantation on retinopathy have surfaced to date. Investigators at the University of Minnesota report that retinopathy stabilizes in many cases but progresses in others (40 per cent) post-transplant. That it may not improve despite normoglycemia indicates that it may have reached a self-propagating stage prior to transplantation.¹²² Proliferative changes can progress to proliferative retinopathy in the presence of euglycemia. Therefore, retinopathy is not yet an inclusive factor for pancreatic transplantation in preuremic type I diabetic patients,¹⁵² although recent data are showing improved¹ or stabilized¹⁵⁰ visual acuity. Stabilization occurs approximately 3 years after pancreatic transplantation (Sutherland DER, personal communication).

Successful transplantation accompanied by significant improvements in physical and psychosocial status may be followed by a period of noncompliance with therapy. Whereas patients had previously been most cooperative with the transplant team, who offered them their only hope of an improved life, they may become hostile and uncooperative.⁹¹ Furthermore, suicide accounts for a significant number of deaths following rejection of pancreatic grafts.¹³⁶

Surgeons at the University of Minnesota have performed pancreas transplants from LRDs since 1979. The procedure is done sequentially following successful renal transplantation from the same donor. Graft survival rates are higher than with cadaveric grafts and are improving with time and experience.¹⁴¹ For the donor, however, the retrieval procedure is not without significant complications, posing significant ethical problems.¹¹⁸ Long-term follow-up of large numbers of recipients and donors is needed to fully demonstrate the benefits of this procedure. Early results are promising, and sequentially transplanted allografts have been shown to reverse the early diabetic changes that occur in transplanted kidneys. The Swedish experience¹⁸ with three mothers, who donated pancreatic tissue to children, reveals more significant deterioration in exocrine and endocrine pancreatic function than has been seen by the Minnesota team, which uses sibling donors. Thus, donor age may be an important factor in the metabolic consequences of living hemipancreas donation.¹⁸

The University of Minnesota, currently the center having the larg-

est series of pancreatic transplants, performed pancreatic transplants alone in 110 nonuremic, nonkidney (NUNK) recipients between July 1978 and January 1988.¹⁴⁵ Very rigorous selection criteria were applied to all potential candidates for NUNK PTA. All had at least one microangiopathic complication of diabetes that was deemed more severe or was progressing to a stage more severe, than the potential side effects of chronic immunosuppression, or they had such extreme difficulty with metabolic control that they were handicapped in the performance of routine daily activities. The technical failure rate was 27 per cent; a similar number of grafts were rejected later. The pancreas graft survival rate in NUNK recipients was lower than for the combined renal pancreatic procedure or for pancreas transplantation following renal transplantation, possibly because uremia in itself is immunosuppressive and blunts the allogenic response.¹⁴⁵

SUMMARY

The future of pancreatic transplantation for potentially eliminating type I DM as a major health hazard promises to be fascinating. The development of less toxic immunosuppressive regimens would allow broader applications of the procedure as well as possibly eradicating type I DM relatively early. Transplantation of cultured fetal pancreas cells may become a reality as a successful graft technique. Earlier means of detecting pancreatic rejection are currently under investigation and should come to fruition. In nonuremic individuals, the results of pancreatic transplantation on reversing or stabilizing the microangiopathic complications of type I DM are encouraging but have not yet produced definitive conclusions. Therefore, the procedure must still be considered experimental. On the other hand, combined pancreatic renal transplantation or pancreas transplantation after renal transplantation, a two-stage procedure, should be offered to all type I diabetics who are candidates for renal transplantation.

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Anesthesia for Liver Transplantation

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In 1963, Starzl performed the first liver transplantation in a child with a hepatoma.¹¹² Since that time, pioneering work has been led by programs in Pittsburgh; Cambridge, England; and Hanover, Germany. A dramatic change occurred in 1982 and 1983, when the surgical procedure was simplified by the use of veno-venous bypass, the anesthetic management was improved, and the clinical use of cyclosporine provided a breakthrough in immunosuppression.¹¹³ The procedure is now considered therapeutic, with 1-year survival at about 70 per cent and 5-year survival reaching 50 per cent. Currently, more than 60 centers exist in the United States. About 10 of these perform more than 50 cases a year, the largest number (more than 500 cases in 1988) at the University of Pittsburgh. Over the next decade, further proliferation of centers will be followed by a similar increase in number of liver transplantations because of (1) broadened indications, (2) simplified perioperative care with better understanding of the associated pathophysiology, (3) training of more specialists, (4) availability of more donor organs, and (5) the possible addition of new immunosuppressive agents.

The goal of liver transplantation is to prolong the productive life of patients with irreversible end-stage liver disease, whose life expectancy would otherwise be very short. This goal has been achieved in a large number of patients, many of whom enjoy a normal, productive life.¹²⁷

The contribution of liver transplantation to medicine has been astonishing. When a grafted replaces a diseased native liver, it not only restores hepatic function but also corrects many disease states. Liver transplantation has been performed in hemophiliac patients to treat chronic active hepatitis contracted by transfusion of factor VIII concentrate. In this setting, it not only restores hepatic function but also treats hemophilia. This information leads us to believe that the liver is a major production site of factor VIII.¹² Other diseases curable by liver transplantation include many inborn errors of metabolism,

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hypercholesterolemia, Wilson's disease, and hemochromatosis, to name a few.¹⁰⁴ Thus, liver transplantation provides a window for understanding the liver's physiologic role as well as for treating previously incurable diseases.

Liver transplantation has changed anesthesia practice. The coexistence of severe coagulopathy helped us to understand the monitoring and treatment of coagulation.⁵¹ Frequently required massive blood transfusion impelled us to improve the mode of transfusion and prepare for its complications.¹⁰² An excellent clinical anhepatic model helped to reveal the metabolic function of the liver.^{76, 84} The complex high-output and low-resistance cardiovascular system seen in these patients presents a challenge to members of the anesthesia team.

This article describes the anesthetic management of liver transplantation in adults. Most aspects also apply to the care of patients with hepatic dysfunction undergoing other major surgeries.

ANATOMIC CONSIDERATIONS

The liver is the largest organ in the body, weighing 1400 to 1600 g in adults. It is a continuous mass but is divided into two lobes by the line of the falciform ligament. The right lobe is six times larger than the left and contains two smaller lobes: the caudate and the quadrate lobes. Fibrous septae do not exist, and intercommunications of the vascular and biliary systems are found between the lobes. The liver is connected to the diaphragm, abdominal wall, stomach, and duodenum by five ligaments: falciform, coronary, hepatorenal, right triangular, and left triangular ligaments, all containing blood vessels, lymphatics, and a nerve plexus.

The liver receives 25 per cent of total cardiac output and a dual blood supply. The portal vein supplies 65 to 80 per cent of the blood flow and the hepatic artery, 20 to 35 per cent. However, tissue oxygenation depends on both the saturated hepatic arterial blood and less saturated portal venous blood. These vessels join together at the porta hepatis and branch out to the right and left lobes. Venous blood drains to the inferior vena cava via several hepatic veins. The inferior vena cava is arbitrarily divided into three portions: suprahepatic, intrahepatic, and infrahepatic. Hepatic arterial blood flow is controlled mostly by arteriolar tone, which responds to changes in portal flow and, thus, alterations in total blood and oxygen supply to the liver. For example, a decrease in portal flow is associated with an increase in hepatic arterial blood flow. This compensatory mechanism is influenced by neural, myogenic, metabolic, and washout effects.^{41, 68} Portal venous blood flow is controlled by the arterioles of the splanchnic organs. Intrahepatic portal flow is regulated by the tone of postsinusoidal sphincters, which respond to alpha agonists. The liver plays a significant role as a blood reservoir, and venous return to the heart is influenced by alpha-sympathetic nerve fibers existing in the hepatic veins.

Histologically, the liver is composed of functioning units, the liver acini. The acinus is a small parenchymal mass, irregular in size and shape, and arranged around an axis consisting of a terminal hepatic arteriole, portal venule, bile ductule, lymph vessels, and nerves. Each acinus is divided into three zones according to their proximity to the axial terminal vascular branches. Hepatocytes in zone 1 are closest to the vascular branches and receive oxygenated blood and nutrients. Peripherally located hepatocytes in zones 2 and 3 receive less oxygenated and nutrient blood and are prone to ischemic damage. The biliary system develops from the acinus, following the pattern of the vascular tree, and forms a bile duct and common bile duct. Collateral vascular channels are seen, because the liver is an outgrowth of the gastrointestinal tract and shares the vascular arcade. Gradual occlusion of the hepatic artery generates a collateral circulation via the right and left gastric, gastroepiploic, gastroduodenal, supraduodenal, and superior and inferior pancreaticoduodenal arteries. Collateral circulation of the portal vein also exists. In extrahepatic portal obstruction, portal blood flow is maintained via deep cystic veins, epiploic veins, diaphragmatic veins, paraumbilical veins, veins in the wall of common bile duct, and veins of the suspensory ligament. In intrahepatic portal obstruction, portal venous flow becomes directed toward the stomacho esophageal, portorenal, and hemorrhoidal plexus, paraumbilical veins, and intrahepatic Eck's fistulae. The nerve supply to the liver consists of the anterior and posterior nerve plexus. The anterior nerve plexus derives from bilateral ganglia at T7 to T10, the left vagus, and the right phrenic nerve, whereas the posterior is a bundle of nerve fibers ramifying around the portal vein and bile ducts. The arteries are innervated exclusively by sympathetic fibers, whereas the bile ducts are innervated by sympathetic and parasympathetic fibers.

The liver consists of hepatocytes, endothelial cells, and Kupffer cells. Hepatocytes carry out complex hepatic metabolism. Endothelial cells contain pinocytotic vesicles, mitochondria, and endoplasmic reticulum. Kupffer cells are fixed macrophages and contain phagocytic vacuoles with lysosome. They clear bacteria, endotoxins, pigments, and cellular debris, and participate in iron metabolism.

PATHOPHYSIOLOGIC CONSIDERATIONS

Although candidates for liver transplantation often have multi-system organ failure, the extent of their disease falls into one of three groups with varying degrees of hepatic dysfunction. Patients with neoplasms may have relatively normal function of the liver and other organs. At the other extreme, patients with postnecrotic cirrhosis have severe hepatocellular disease. These patients show characteristic signs of end-stage liver disease and develop multiple organ involvement. Patients with cholestatic disease fall somewhere in between, with better hepatic function than patients with hepatocellular disease.

The Central Nervous System

Hepatic encephalopathy occurs commonly in advanced liver disease and is known to be associated with an increased blood ammonia level and accumulations of mercaptans, short-chain fatty acids, false neurotransmitter, and gamma aminobutyric acid.^{34, 91, 103, 117} Patients may exhibit subtle confusion (stage 1), gross mental confusion (stage 2), somnolence and stupor (stage 3), or deep coma with response only to pain (stage 4). Several factors worsen encephalopathy: diuretic therapy, gastrointestinal hemorrhage, infection, and further hepatic damage. Brain edema transpires in 50 per cent of patients with acute fulminant hepatic failure,⁴⁰ and some degree of cortical atrophy and nonspecific alteration in the EEG take place in chronic liver disease. When severe coagulopathy occurs, intracranial hemorrhage may develop.

The Cardiovascular System

The cardiovascular system in severe liver disease is characterized by a hyperdynamic circulatory state, with high plasma volume, high cardiac output, and low vascular resistance.^{15, 79} Low vascular resistance results from vasodilation in the extremities secondary to increased circulating levels of vasodilator substances either produced or not detoxified by the liver, for example, glucagon, vasoactive intestinal polypeptide, or ferritin. Extensive arteriovenous shunting follows the development of pulmonary arteriovenous fistulae and mediastinal- and paraesophageal-pulmonary venous communications.^{11, 19} Arteriovenous shunting and decreased oxygen consumption produce an increased mixed venous oxygen saturation. High cardiac output is frequently maintained with relatively normal arterial and venous filling pressures. The sympathetic response to baroreceptor stimulation appears to be impaired, and patients are resistant to norepinephrine.⁷⁴ Resting ventricular function may be normal in many patients, but these individuals may not tolerate added stress or an increase in afterload.⁶ Left ventricular ejection fraction remains within or greater than the normal range.^{61, 85} However, relatively normal ejection fraction in the presence of decreased afterload does not necessarily indicate adequate cardiac performance. Ventricular performance is frequently impaired in patients with Laennec's cirrhosis, Wilson's disease, and hemochromatosis.^{18, 67, 73} Some degree of mitral regurgitation may be seen owing to the hyperdynamic state. Coronary artery disease is relatively uncommon in patients with liver disease.⁹⁹ In recipients, pulmonary hypertension sometimes results from pulmonary emboli, increased plasma volume, or release of vasoconstrictive substances.⁶⁹ Unsuspected cardiomyopathy, myocardial ischemia leading to infarction, pericarditis, and pericardial effusion have been seen during liver transplantation.

The Pulmonary System

Arterial oxygen tension and oxygen saturation of hemoglobin are frequently decreased²³ owing to ventilation-perfusion mismatch and

impairment of hypoxic pulmonary vasoconstriction.²⁴ Also, increased intrapulmonary right-to-left shunting and a shift in the oxygen-hemoglobin dissociation curve contribute to arterial desaturation.⁶²

Ventilation often becomes inadequate because of poor nutrition, atelectasis, and resistance to excursion of the diaphragm by ascites and pleural effusion.⁶⁶ Tidal volume, vital capacity, and functional residual capacity are decreased; yet, compensatory tachypnea can result in respiratory alkalosis. Currently, we do not consider a patient with severe hypoxemia to be a candidate for surgery. Adult respiratory distress syndrome sometimes arises in those with severe hepatocellular dysfunction, possibly secondary to the decreased hepatic clearance of endotoxin. Adult respiratory distress syndrome associated with hepatic failure improves dramatically after successful liver transplantation.⁸⁶

Hepatic Function

Hepatic function includes (1) regulation of blood volume to maintain normovolemia; (2) excretion of bile, metals, and dyes; (3) metabolism of carbohydrates, fat, protein, minerals, and vitamins; (4) detoxification; (5) hemopoiesis; and (6) destruction of red blood cells. The important hepatic functions relevant to anesthesiology are metabolism of carbohydrate and protein, including coagulation factors, and biotransformation of drugs.

Glucose intolerance and insulin resistance are known to occur before, at, and beyond the receptor level.³⁶ Both hypersecretion and delayed clearance of insulin account for a high circulating insulin level. In those with cirrhosis, a high blood glucagon level results from hypersecretion and effects of portasystemic shunting.⁷⁷ However, severe hypoglycemia occurs during acute fulminant hepatic failure, owing to the depletion of glycogen storage, decreased gluconeogenesis, and other hormonal interactions.¹⁰¹ Administration of glucose prevents hypoglycemic coma in such patients.

Although the liver serves as the major site for drug biotransformation, the effect of hepatic dysfunction on drug disposition has not been consistent or predictable because liver disease can affect the absorption, tissue distribution, and protein binding of drugs as well as hepatic metabolism. Therefore, careful titration of drugs is mandatory. Low plasma levels of pseudocholinesterase can occur in patients with hepatic failure; yet levels usually normalize after successful transplantation.⁴ A decrease in protein binding augments the effect of certain drugs, such as thiopental.⁴² However, increased binding to globulin and an increased volume of distribution decrease the sensitivity to pancuronium and D-tubocurarine.^{29, 123} Decreased microsomal enzyme activity prolongs the elimination half-life of most lipophilic drugs, such as pancuronium, thiopental, morphine, meperidine, fentanyl, and diazepam.^{48, 64, 65, 109, 110} A recent pharmacokinetic study of alfentanil showed that cholestatic disease may not alter its metabolism. Extrahepatic metabolism of drugs may occur, as demonstrated by urinary excretion of morphine metabolites in an anhe-

patic animal model and the near normal elimination half-life of fentanyl in some patients with hepatic failure.⁵⁹ The half-life of lidocaine increases threefold because of decreased hepatic clearance and increased volume of distribution.¹¹⁸ Branch and coworkers¹⁶ noted an eightfold increase in the half-life of propranolol in patients with cirrhosis.

The Hematologic and Coagulation System

Hypochromic, microcytic, or macrocytic anemia invariably develops in cirrhotic patients from malabsorption of iron and folic acid, frequent variceal bleeding, and hypersplenism.¹¹¹ Furthermore, changes in lipid metabolism of cell membranes shorten red cell survival.

In severe hepatocellular disease, coagulopathy ensues from malabsorption of substrates, defective hepatic synthetic function, and inadequate hepatic clearance of activated coagulation factors.⁹⁸ All coagulation factors decrease except fibrinogen and factor VIII. The fibrinogen level is frequently higher than normal, but dysfibrinogenemia often follows the formation of abnormally structured fibrinogen.⁸³ The clinical significance of dysfibrinogenemia is unclear. Factors VIII:Ag and VIII:vW are produced in the vascular endothelium, whereas factor VIII:c production possibly takes place in the liver. Activation of the vascular endothelium, the stress response, and impaired catabolism account for higher than normal levels of factor VIII.⁴³ In addition, levels of Fletcher factor, Fitzgerald factor, alpha 1-antitrypsin, alpha 2-macroglobulin, antithrombin III, and plasminogen decrease. Thrombocytopenia occurs in 70 per cent of cases and is frequently associated with impaired platelet function. The latter results from a preponderance of small, hypofunctional platelets.^{7, 60} Increased fibrinolytic activity results from decreased production of antiplasmin and inadequate clearance of tissue plasminogen activators.^{35, 93} Fibrin degradation product levels become positive in one third of cases, and euglobulin lysis time is frequently shortened. Low-grade intravascular coagulation can occur by activation of the coagulation system, but its significance remains unknown. The clinical significance of coagulopathy is well demonstrated by the correlation between the preoperative degree of coagulopathy and intraoperative blood product requirements: patients with hepatocellular disease and poor preoperative coagulation profile require more blood products during surgery.¹³ The vascular phase of coagulation is as important for hemostasis as the coagulation cascade, and patients with liver disease appear to have impairment of the vascular phase.

The Renal System

Hepatorenal syndrome, acute renal failure, or glomerulonephritis frequently occurs with severe liver failure. Characteristic renal findings include sodium retention, decreased water clearance, and decreased concentration capacity. Kidney dysfunction is associated with hyperaldosteronism, increased sympathetic tone, enhanced antidi-

uretic activity, increased conjugated bilirubin levels, and altered activity of renal prostaglandins, the renin-angiotensin system, or the kallikrein-kinin system.^{8, 9, 27, 115, 126, 128} The hepatorenal syndrome improves after successful liver transplantation,⁴⁹ but differentiation of hepatorenal syndrome from other renal diseases proves very difficult because of the frequent use of complex diuretic therapy. In general, patients with the hepatorenal syndrome demonstrate low urine sodium concentration (<10 mEq per L), high urine-to-plasma creatinine ratio (>30), and high urine osmolality (>100 + plasma osmolality).³³ Inadequate intravascular volume and nephrotoxicity secondary to cyclosporine also impair renal function.⁶³

Fluids, Acid-Base Balance, and Electrolytes

In general, blood volume increases by 10 to 20 per cent above normal values.³² However, intravascular volume can be substantially depleted by the continuous formation of ascitic fluid and by diuretic therapy to treat ascites. On the other hand, rapid administration of fluid or blood products may cause volume overloading. A common finding is hyponatremia, emanating from increased antidiuretic hormonal activity and impaired renal water excretion. Preoperative correction of hyponatremia is very difficult and, when undertaken without hemodynamic monitoring, may significantly derange the intravascular blood volume. Chronic hypokalemia and depletion of total body potassium frequently follow diuretic therapy, inadequate potassium intake, and continuous loss from vomiting and diarrhea.³ Because of preoperative difficulties in treating hypokalemia and because hyperkalemia inevitably occurs with reperfusion of the grafted liver,²¹ we avoid acute correction of hypokalemia. One often sees hyperkalemia in patients with moderate-to-severe renal dysfunction, necessitating dialysis. During massive transfusions, ionized hypocalcemia may require administration of CaCl_2 or calcium gluconate. The presence of hyperphosphatemia and hypomagnesemia has been described, but their clinical significance in patients undergoing liver transplantation is unknown.⁸⁰

In uncomplicated chronic cirrhosis, metabolic alkalosis commonly associates with hyperaldosteronism, vomiting, and diarrhea, and it frequently superimposes on respiratory alkalosis. In contrast, metabolic acidosis is a common acid-base disorder in those with acute fulminant hepatitis, rapidly progressing hepatic failure, or unrecognized infection.

SURGICAL CONSIDERATIONS

As is true of all surgical procedures, teamwork between surgeon and anesthesiologist is an absolute necessity for successful intraoperative care of patients undergoing this stressful and complex surgery. The importance of a clear understanding of the surgical proce-

dures by the anesthesiologist and a thorough appreciation of the physiologic stress involved by the surgeon cannot be overstressed.

Orthotopic Liver Transplantation

Orthotopic liver transplantation, the most common transplantation procedure, is performed by transplanting the donor liver after hepatectomy at the same site. It is divided into three distinctive stages. The *preanhepatic stage* is from skin incision to the skeletonization of the hepatic vasculature. During this period, surgical bleeding is common because of the numerous collateral channels and the difficulty encountered during hilar dissection, particularly in patients who have had previous abdominal surgery. Additionally, surgical manipulation and compression of the inferior vena cava (IVC), portal vein, and hepatic artery may acutely disrupt venous return and cardiac output.

The *anhepatic stage* begins with hepatectomy and ends when vascular anastomosis of the IVC and portal vein is complete. Cross clamping of the IVC and portal vein for hepatectomy reduces venous return to as low as 50 per cent of the cardiac output, and severe negative hemodynamic effects can occur at this time.⁹⁴ Three different techniques are currently in use during the anhepatic stage. The simple cross-clamping technique requires no additional measures; the IVC and portal vein are cross clamped for hepatectomy and revascularization. The resulting decrease in venous return and cardiac output often necessitates administration of fluid or vasopressors such as dopamine. Generally, the recipient tolerates the brief period of hypotension and low cardiac output. However, vascular clamping may cause visceral and renal venous congestion, resulting in intestinal swelling and hematuria. This technique, although it is not physiologic, appears to be effective when performed by skillful surgeons in selected patients.¹²²

The second technique, veno-venous bypass, has been used successfully to avoid physiologic stress¹⁰⁶ and is now most commonly used. A cannula is inserted in the portal and femoral veins, and the drained blood is returned to the axillary vein with a centripetal pump (Biopump, Biomedicus, MN).⁴⁴ The system does not require systemic heparinization, and a small dose of heparin (1000 to 2000 U) is added in the bypass cannula to prevent thrombosis during cannulation and preparation of bypass. It has a flow rate of up to 40 per cent of cardiac output, and hemodynamic changes generally do not occur when bypass flow is adequately maintained. However, bypass flow may decrease when the cannulae are obstructed by the vessel wall, the tubing becomes kinked, the centripetal force is too excessive, or cardiac output is low.¹⁰⁷ An inadvertent decrease in bypass flow should be corrected to maintain hemodynamic stability.

Before completion of the infrahepatic inferior vena caval anastomosis, the donor liver is flushed with lactated Ringer's solution (300 to 500 ml) via the portal vein to remove preservation solution, air, and metabolites. A large amount of potassium can be removed from the donor liver by flushing with 100 ml in children and 200 ml in adults.²²

When anastomosis of the IVC is complete, the portal cannula is removed for portal venous anastomosis. The resulting femoral-axillary bypass without portal venous flow decreases bypass flow and cardiac output. For prevention of thromboembolism, Denmark and others²⁶ recommend a minimum bypass flow of 1 L per minute.

Femoral venoarterial bypass was developed in Cambridge. This technique bypasses femoral venous blood to the femoral artery, to avoid congestion of the inferior vena cava,²⁰ but it does not decompress the portal system. Furthermore, bypassing desaturated blood to the arterial system may interfere with oxygen delivery to tissues.³⁰

The *neohepatic stage* begins with reperfusion of the grafted liver by release of clamps on the portal vein, infrahepatic IVC, and suprahepatic IVC. Unclamping of the portal vein and infrahepatic IVC causes an acute decrease in preload, and unclamping of the suprahepatic IVC transiently increases preload and blood pressure. This acute change is followed by characteristic hemodynamic changes that have been termed the "postreperfusion syndrome."² Hepatic arterial reconstruction follows, as the hepatic artery of the grafted liver is connected to the hepatic artery or the aorta of the recipient. Biliary reconstruction is carried out with duct-to-duct anastomosis (choledoch-choledochostomy). Choledochojejunostomy to a Roux-en-Y limb may be used for patients with inadequate biliary drainage caused by biliary atresia, biliary cirrhosis, or sclerosing cholangitis. Meticulous hemostasis is required before closure of the abdominal cavity.

Occasionally, hepatectomy can be performed by peeling the liver off the IVC without dissecting the IVC (piggyback liver transplantation). This technique is simpler in principle, because hepatectomy does not require cross clamping of the IVC, and systemic venous blood return is maintained. Reconstruction consists of anastomosis of the portal veins, hepatic arteries, and suprahepatic IVC of the donor liver to the hepatic vein of the recipient. However, total hepatectomy without dissection of the hepatic portion of the IVC can be technically difficult, and hemodynamic instability occurs from frequent compression of major vessels, no portal venous flow, and severe surgical bleeding.

Heterotopic (Auxiliary) Liver Transplantation

In heterotopic liver transplantation, the donor liver is placed in the paravertebral gutter or in the pelvis without removing the diseased liver.³⁷ However, this technique is frequently complicated by atrophy of the grafted liver from insufficient portal blood supply and less than optimal hepatic arterial blood flow. Therefore, it is reserved for patients who have reversible liver disease or who are at extremely high surgical risk, such as those with extensive previous surgery in the right upper quadrant or a thrombosed portal vein.

Organ Preservation Technique

Continuous perfusion and simple hypothermia have been used for preservation of the donor liver. Continuous perfusion is used rarely, however, because complex equipment is required, vascular

resistance increases gradually, and outcome is not superior to that of simple hypothermia. The simple hypothermic preservation technique consists of irrigation of the hepatic vascular tree and suspension of the liver in ice-chilled preservation solution. The preservation solution duplicates intracellular electrolyte composition, containing high potassium and low sodium concentrations. Collins solution provides a clinically satisfactory cold ischemia time of 10 hours.¹⁷ Recently, the University of Wisconsin solution has been used successfully to extend the allowable cold ischemia time to 24 hours.^{50, 119} These preservation methods can affect the recipient's homeostasis. A rapid influx of acidic and metabolite-rich solution as the grafted liver is reperfused may cause hemodynamic instability. Addition of a cell-membrane stabilizer (chlorpromazine) to Collins solution results in prolonged hypotension after reperfusion in the recipient.⁵⁷

ANESTHETIC CONSIDERATIONS

Preoperative Evaluation

Preoperative evaluation is performed in two stages. All candidates for liver transplantation are examined by anesthesiologists to rule out any condition contraindicating surgery or to determine aspects of the physical condition that can be improved. They are then evaluated at a joint meeting with hepatologists, surgeons, anesthesiologists, intensivists, and nurses. A brief second examination is performed immediately before surgery when a donor organ has been identified. During these preoperative evaluations, perioperative care is explained to the patient and family to reassure them and to obtain their maximal cooperation.

Preoperative evaluation includes the information required for other surgical procedures and the following additional information.

General Physical Status. Because of poor nutritional status, encephalopathy, and ascites, the physical activity of liver recipients is frequently impaired. Recipients are classified according to their physical performance: status 1, does not require hospitalization; status 2, requires hospitalization; status 3, bound to the intensive care unit because of hepatic disease state; and status 4, acute fulminant hepatic failure, anhepatic or near anhepatic. Although the relationship between preoperative physical status and postoperative outcome is not clear, every effort should be made to improve physical status, if possible.

Central Nervous System. Frequently, EEG, evoked potential studies, and computed tomogram of the brain are advised to rule out any organic disease mimicking hepatic encephalopathy. Any organic changes in cerebral function may contraindicate liver transplantation. In patients with acute hepatic failure, an increase in intracranial pressure should also be ruled out.

Cardiovascular System. History and physical examination are

the most important aspects of the preoperative evaluation, because exercise tolerance is very difficult to elicit or meaningless when fatigue, cachectic physical state, and ascites prevent significant activity. Any history of cardiovascular impairment warrants further investigation because less than optimal cardiovascular function and decreased tissue perfusion may lead to multiple organ failure, hepatic ischemia, and death. Potential cardiovascular risk factors include any arrhythmia, hypertension, hypotension, cardiomyopathy, ischemic heart disease, and pericarditis. Patients with alcoholism, Wilson's disease, hemochromatosis, and hypercholesterolemia require a complete work-up to rule out myocardial disease.^{67, 70} Echocardiography evaluates ventricular wall motion, valvular function, and the presence of pericardial effusion. Left ventricular ejection fraction can be estimated by means of echocardiography or multiple gated scan. Coronary angiography rules out significant coronary artery disease.

Pulmonary System. All patients with a history or clinical signs of pulmonary dysfunction undergo pulmonary function testing. Patients with pulmonary disease are identified in the early stage and attempts are made to improve gas exchange, because prolonged mechanical ventilatory support and pulmonary infection represent major postoperative complications. Unless ascites and pleural effusion severely impair gas exchange, we defer drainage of fluid until the intraoperative period. Any type of pulmonary infection contraindicates surgery because of the high incidence of life-threatening postoperative pneumonia that occurs in immunosuppressed patients. On the other hand, adult respiratory distress syndrome secondary to liver disease does not contraindicate surgery.

Hepatic System. ICG clearance test, prothrombin time, bilirubin level, SGOT, SGPT, and an ammonia level provide clues to the degree of hepatocellular disease. Serologic tests for hepatitis and AIDS are reviewed to avoid contamination of health care personnel and the surgical suite. Patients with abnormalities in the hepatic vasculature, such as a thrombosed portal vein, abnormal hepatic arterial anatomy, or any previous portal decompression procedures are placed at high surgical risk.

Coagulation System. A preoperative coagulation profile evaluates the degree of coagulopathy. Preoperative plasmapheresis improves coagulation⁸⁹ but requires too much time for the surgical emergency. Thus, the anesthesia team manages coagulation intraoperatively with adequate monitoring of the coagulation and cardiovascular systems. Early identification of blood type and the presence of any antibodies is a must.

Renal System: Fluids and Electrolytes. Renal dysfunction of prerenal origin mandates correction. Patients with severe azotemia or hyperkalemia require preoperative dialysis. Simultaneous liver and kidney transplantation can be considered for patients with coexisting primary renal disease.¹¹⁴ Fluid and electrolyte imbalance warrants treatment, although complete resolution may not be possible preoperatively. Furthermore, patients with hyponatremia (120 to 130 mEq

per L) and hypokalemia (2 to 3 mEq per L) have undergone surgery without sustaining significant clinical sequelae.⁸⁰ One must remember that hyperkalemia invariably occurs during transplantation.

Premedication

We do not routinely give premedicants because of hepatic encephalopathy and possible hematoma formation following intramuscular injection. Thorough preoperative counseling frequently suffices for patient preparation and allows the alert individual to interact with family members before surgery.

Anesthetic Preparation

Surgical and anesthetic management of each patient is discussed with members of the patient care team. Medications and equipment required for liver transplantation are listed in Table 1. Tight control of physiology is essential to maintain homeostasis. Therefore, a system for rapid assessment of blood-gas tensions, acid-base state, electrolytes, serum ionized calcium, blood glucose, and lactate should be in place.

Positioning and Monitoring

The recipient is placed on a well-padded operating table (containing a warming blanket) with both arms abducted and resting on padded armboards. Venous access entails an 8.5 French catheter in the right antecubital vein and another large catheter in the left internal or external jugular vein. We insert an 18-gauge cannula into the right femoral artery for blood pressure monitoring while placing a 20-gauge cannula into the right radial artery (after Allen's test) for blood sampling and back-up pressure monitoring. We then identify the right internal jugular vein for placement of an oximetric pulmonary artery

Table 1. *Equipment Necessary for Liver Transplantation*

Anesthesia gas machine with compressed air supply
Volume ventilator
Inspired gas humidifier
Multiple-channel vital sign monitor
Automated data acquisition system
Cardiac output computer
Online mixed venous oxymetry
Pulse oximeter
Mass spectrometer
Thrombelastograph
Blood pump and blood warmer
Rapid infusion system
Autotransfusion system
Cardiac defibrillator
Warming blanket
Supply cart
Telephone

catheter. Cardiograph electrodes are secured with tape away from the surgical field, and the pulse oximeter probe rests on the right index fingertip. An indwelling urinary catheter, rectal thermistor, esophageal stethoscope, and nasogastric tube are inserted. The upper extremities and head are wrapped with vinyl covers to prevent heat loss. The occiput is placed on a sponge pad and the body is positioned to prevent any pressure injury.

Induction and Maintenance

After securing intravenous and radial artery cannulae, anesthesia is induced with a rapid sequence approach, using preoxygenation and cricoid pressure. One must remember that delayed gastric emptying often exists in patients with liver disease, especially those taking cyclosporine orally. We most commonly use thiopental (4 mg per kg) for induction but have successfully used etomidate (0.3 to 0.5 mg per kg) or ketamine (2 mg per kg). Following hypnosis, succinylcholine (1 to 2 mg per kg) facilitates endotracheal intubation after a small dose of nondepolarizing agent to prevent fasciculation. Confirmation of proper endotracheal tube position prevents unrecognized unilateral ventilation. Then mechanical ventilation begins with an oxygen/air mixture ($F_{iO_2} = 0.5$), PEEP (5 cm H_2O), and P_{aCO_2} levels of 35 to 40 mm Hg.

Anesthesia is maintained with an inhalation agent or narcotics. Most anesthesiologists avoid nitrous oxide in these cases, because it depresses the myocardium, increases the size of air emboli, depresses bone marrow, and distends bowel loops.^{31, 90} Isoflurane receives the most widespread use because hepatotoxicity has not been reported. Additionally, the degree of cardiovascular depression and biotransformation is less than with halothane and enflurane.^{46, 47, 116, 125} The possibility of fluoride-induced nephrotoxicity⁸⁷ recommends against the use of enflurane. In our practice, narcotics (fentanyl or morphine) are used for maintenance or as an adjunct to isoflurane. This procedure requires profound, long-lasting muscle relaxation; pancuronium provides excellent results. The use of vecuronium or atracurium entails frequent dosing and significant expense, although both agents have been used safely. Doxacurium, a newer muscle relaxant, also appears to be satisfactory and without prolonged drug effects.³⁹ Long-acting sedatives (such as lorazepam) are used for amnesia.

Intraoperative medications include antibiotics and immunosuppression. At the University of Pittsburgh, ampicillin (1 g) and cefotaxime (1 g) are given every 4 hours during surgery. Patients receive a single bolus of methylprednisolone (1 g) and a slow infusion of cyclosporine (2 mg per kg) after reperfusion.

Intraoperative Management of Physiology

The anesthesia team must provide critical care of the patient while inducing and maintaining adequate analgesia, amnesia, and muscle relaxation. Therefore, intraoperative management focuses on maintaining the best possible physiologic conditions.

Central Nervous System. Currently available monitoring proves inadequate for understanding intraoperative changes in CNS status, although a rapid postoperative recovery from stage 4 coma reflects dramatic improvement in CNS function. On the other hand, intracerebral hemorrhage sometimes occurs in the early postoperative period, and increased intracranial pressure can develop during acute fulminant hepatitis. Hence, Potter and others⁹⁷ suggest intraoperative monitoring of intracranial pressure. Other possible causes of coma include hyperosmolarity and cerebral air emboli, which result from inevitable intraoperative air emboli.

Cardiovascular System. Intraoperative changes in physiologic variables are shown in Table 2. In the beginning of surgery, a complete hemodynamic profile measures baseline cardiovascular performance. High filling pressures are noted occasionally, possibly caused by fluid overloading, massive ascites, pleural effusion, pericardial effusion, or pulmonary hypertension. A chest tube, placed after the peritoneal cavity has been opened, drains pleural fluid. If necessary, the surgeon also makes a pericardial window when suspecting pericardial effusion. Marginal cardiac performance necessitates a vasopressor (for example, dopamine, 2 to 5 μg per kg per minute), although end-stage liver disease may increase the resistance to catecholamines. Alpha-agonists may increase shunt fraction and perturbate tissue perfusion; their effects require further investigation.

The hyperdynamic cardiovascular state continues during the preanhepatic stage, if the anesthesia team adequately replaces intravascular volume losses secondary to surgical bleeding and continuous formation of ascites. Surgical manipulation of major vessels reduces venous return; unexpected or prolonged hypotension requires necessary adjustments of surgical technique. At the end of the preanhepatic stage, caudad traction on the liver to isolate the suprahepatic IVC may cause transient arrhythmia and hypotension.

Table 2. Characteristic Intraoperative Changes in Physiologic Variables

	PREANHEPATIC STAGE	ANHEPATIC STAGE	NEOHEPATIC STAGE	
			EARLY	LATE
Cardiac output	High	Low	High	High
Heart rate	High	High	Low	High
Mean arterial pressure	Normal	Low	Very low	Normal
Filling pressure	Normal	Low	High	Normal
Vascular resistance	Low	High	Very low	Low
Pao ₂	Normal	Normal	Normal	Normal
PCO ₂	Normal	Low	Normal	Normal
Base deficit	Normal	High	Very high	Normal
Serum Na	Low	Normal	Normal	Normal
Serum K	Low	Normal	Very high	Low
Serum Ca ²⁺	Normal	Very low	Low	Normal
Serum citrate	Normal	High	High	Low

The anhepatic stage begins with simple cross clamping of the IVC, portal vein, and hepatic artery, or cannulation of the portal and femoral vein for veno-venous bypass. Simple cross clamping often brings forth significant hypotension. Whereas the role of portal blood flow in total venous return would not seem to be significant, especially in those with significant collateral flow, portal occlusion frequently elicits a hypotensive response. The use of volume expansion and inotropic agents can ameliorate the negative hemodynamic changes associated with vessel clamping. However, volume expansion carries the possibility of fluid overload during reperfusion. Vessel occlusion also promulgates surgical bleeding, hematuria, and congestive ischemia of the bowel.

In contrast to the simple cross-clamping technique, initiation of bypass restores venous return but may produce transient bradycardia and a tall T-wave owing to rapid influx of cold priming solution. Hemodynamic stability depends on the bypass flow exceeding 2.5 L per minute.⁵⁷ Because the patient's intravascular volume serves as the bypass reservoir, bypass flow depends on inflow of blood from the patient to the system. Therefore, events such as hypovolemia, an obstructed cannula, or kinked tubing will limit bypass flow. The anesthesiologist must report perturbations of flow to the surgical team and then clear obstructions, adjust pump motor speed, or restore normovolemia. Occasionally, bypass is terminated by a malfunctioning system, necessitating treatment of acute hypotension and low cardiac output. Other complications of bypass include air emboli from the cannulation site, lacerations of the portal vein, and pulmonary thromboembolism. Surgical bleeding may not be as florid when the portal vein and IVC are decompressed by veno-venous bypass. Upon completion of anastomosis of the IVC, removal of the portal cannula facilitates portal venous anastomosis. During this time veno-venous bypass carries only systemic venous blood (partial bypass), and the resulting hypovolemic state (lasting 10 to 15 minutes) may require intravenous fluids. At this point, we administer fluids cautiously to avoid overloading during reperfusion of the grafted liver. Prior to reperfusion, we correct abnormalities of blood-gas tensions, acid-base state, electrolyte levels, and blood volume status.

Abrupt hemodynamic changes occur on reperfusion of the grafted liver.²¹ Unclamping of the portal vein and infrahepatic IVC decreases preload. This is followed by restoration of venous return on unclamping of the suprahepatic IVC. Within 1 to 5 minutes the "postreperfusion syndrome" takes place,² most commonly consisting of progressive bradyarrhythmia, hypotension, high filling pressures, and decreased systemic vascular resistance.⁶¹ At this time, thermodilution measurements of cardiac output are unreliable owing to the rapid influx of cold preservation solution. Dye-dilution studies show an increase in cardiac output in comparison to the anhepatic stage, but output values remain lower than baseline levels.² A severe form of postreperfusion syndrome (MAP < 70 per cent of baseline) occurs in 29 per cent of cases, occasionally requiring full-scale resuscitation.

To prevent and treat the postreperfusion syndrome, one must understand its etiology. A relationship to an acute influx of hyperkalemic, acidotic, and cold preservation solution from the grafted liver has been suggested. Yet, the level of hypotension does not correlate with the degree of hyperkalemia, and symptoms persist after core temperature returns to 34°C. This indicates causation by vasoactive substances released from the grafted liver. In an animal model, no cardiac arrest occurs when effluent blood from the liver undergoes dialysis before entering the systemic circulation, suggesting that the causative substance is dialyzable.⁷⁸ Postreperfusion syndrome is treated with 5 to 10 µg increments of epinephrine to increase myocardial contractility and to restore heart rate. Calcium chloride (1 g) and sodium bicarbonate (50 mEq) are administered to treat symptoms of hyperkalemia and acidosis. Some clinicians use calcium chloride prophylactically, which maintains cardiac index but does not prevent bradycardia and hypotension.⁸¹ Other methods to treat hyperkalemia (intravenous insulin-glucose) are not necessary, for acute hyperkalemia dissipates within 10 minutes.

Patients recover from this acute hemodynamic insult in the next 5 to 30 minutes but filling pressures stay high for 30 to 120 minutes and systemic vascular resistance remains low. The cause of acutely increased filling pressures is unclear; increased preload, myocardial depression, and air emboli may play a role. Using transesophageal echocardiography, Lichtor et al⁷² detected increased right ventricular size and air emboli in most patients immediately after reperfusion. Clinically significant air emboli occurred infrequently.

Hepatic arterial anastomosis and biliary reconstruction follow reperfusion, and the rest of the neohepatic stage is relatively uneventful. During this period, the patient care team avoids hepatic ischemia by preventing low perfusion pressures, excessive surgical manipulation, high central venous pressure, and use of vasoactive agents. Anastomosis of the hepatic artery to the aorta of the recipient can be associated with diffuse bleeding from retroperitoneal dissection, hemodynamic instability from aortic clamping and unclamping, and bowel ischemia. Manipulation of the liver and major vessels may cause sudden hypotension. Hypertension may accompany the end of surgery and results from fluid overload or cyclosporine, particularly in children. Hydralazine (5 to 10 mg) is sufficient in most cases, but sodium nitroprusside is used for severe hypertension. Closure of the abdominal cavity may increase filling pressures and decrease blood pressure, particularly when the grafted liver is large in relation to size of the abdominal cavity. This may require secondary closure.

Pulmonary System. Proper mechanical ventilation with PEEP improves gas exchange by expanding atelectatic portions of the lung. Drainage of pleural effusion and ascites improves oxygenation dramatically within 1 to 2 hours. We maintain Fio_2 between 40 to 70 per cent to prevent absorption atelectasis and oxygen toxicity. Hourly measurements of arterial blood-gas tensions and monitoring of end-tidal CO_2 levels ensure adequate ventilation. Oxygen consumption

decreases gradually from decreased metabolism during anesthesia, inadvertent hypothermia, and removal of the oxygen-consuming diseased liver. It gradually increases on reperfusion as the grafted liver consumes oxygen. In patients with severe atelectasis, intraoperative bronchoscopy is performed to remove secretions. A volume-limited ventilator is better for patients with poor compliance or adult respiratory distress syndrome.

Lethal pulmonary edema may result from fluid overload or heart failure, and it may not respond to diuretic therapy, especially in patients with marginal renal function. In this situation, phlebotomy combined with an inotropic agent may be effective.

We have reported three cases of fatal pulmonary thromboembolism, all during the anhepatic stage, possibly from migration of pre-existing thrombi in the portal vein or deep venous system via the low-resistance veno-venous bypass system.⁵⁸ Although the associated mortality of pulmonary embolism is very high with or without cardiectomy, early diagnosis is critical in treatment.⁹²

Metabolism and Hepatic Function. Body temperature gradually decreases during the preanhepatic stage from the effects of anesthetics and muscle relaxants, the cold environment, and insufficient energy production by the liver. A further decrease takes place during the anhepatic stage⁵ secondary to the absence of hepatic energy production and heat loss from the veno-venous bypass system. A sudden fall in core temperature (1 to 2°C) accompanies reperfusion, when ice-cold preservation solution enters the systemic circulation. It gradually returns to 34 to 35°C by the end of surgery.

The transfusion of glucose-containing blood maintains blood glucose levels at between 100 to 200 mg per dL.¹²⁰ When blood replacement is minimal, small intravenous doses of glucose avoid hypoglycemia during the preanhepatic and anhepatic stages.²⁸ On reperfusion, sudden severe hyperglycemia occurs⁷⁶ secondary to the massive release of glucose from the donor liver. The glucose level remains high during the neohepatic stage and returns toward normal in 24 hours postoperatively. Persistent hyperglycemia likely relates to impaired glucose re-uptake and glycogenolysis of the grafted liver, very low insulin levels during the anhepatic and neohepatic stages, and an acute increase in glucagon level on reperfusion.²⁸ An additional factor may be insulin resistance, although this possibility requires further investigation.

Function of the grafted liver is detectable about 2 hours after reperfusion: citrate, lactate, and blood glucose levels decrease gradually, coagulopathy improves, and bile is produced. However, preservation injury increases SGOT and SGPT to very high levels (>1000 U); they gradually return toward normal in the postoperative period. Persistent citrate intoxication, lactic acidosis, hyperglycemia, and coagulopathy signal a poor prognosis for grafted liver function.

Fluid Administration and Coagulation. Because of difficulty in obtaining reliable blood loss measurements, hemodynamic variables and urine output guide intraoperative fluid administration. Continu-

ous monitoring of mixed venous oxygen saturation helps to assess preload and cardiac output, assuming that oxygen-carrying capacity, myocardial contractility, and oxygen consumption remain relatively constant.

Hematocrit is maintained at 26 to 28 per cent to reduce red blood cell loss and to improve circulatory rheology. The low oncotic pressure in patients with end-stage liver disease indicates administration of colloid (fresh frozen plasma or whole blood). Interstitial fluid losses are replaced by balanced salt solution. Fluids containing coagulation factors are employed to prevent dilution coagulopathies, especially in patients with low levels preoperatively. We achieve this goal by using a constant fluid mixture (red blood cells: fresh frozen plasma: Plasmalyte A = 2200:300:250 ml) in a rapid infusion system while other intravenous catheters are kept open with electrolyte solution (Fig. 1; Table 3).⁵¹ A calcium- and glucose-free isotonic electrolyte solution avoids hyperglycemia and clot formation in the fluid mixture. This fluid mixture yields hematocrit values of 26 to 28 per cent, coagulation factor levels greater than 30 per cent of normal (except factor V), and relatively normal electrolyte concentrations (except high potassium levels from banked blood). This fluid mixture minimizes body weight gain and provides adequate hydration. Intraoperative hemofiltration may decrease lung water volume,¹²¹ but the same goal can be achieved by minimizing infusion of free water.

Massive transfusion is common during liver transplantation—up to 500 to 700 ml per minute or 300 U of red blood cells (RBC) in 12 hours.¹³ Even in cases that require less than 10 U of RBC, rapid transfusion is necessary to maintain normovolemia. We employ a rapid-infusion system that delivers prewarmed, premixed blood with a controllable and rapid rate (developed by Sassano, University of Pittsburgh, manufactured by Haemonetics Inc; see Fig. 1).¹⁰² Four large spikes are attached at the top of a cardiectomy reservoir (2.5 L capacity), which is lined with a 170 μ m filter, for rapid transfer and mixing of blood products and fluids. The reservoir is connected to a roller pump that delivers up to 1.5 L per minute with less than 300 mm Hg line pressure, when two large bore tubes are connected to two 8.5 French catheters. Speed of transfusion is adjusted in one of two ways: (1) a continuous infusion mode with variable rate of administration, or (2) a mode delivering 100 or 500 ml boluses at a rate of 400 ml per minute. The blood passes through a heat exchanger column that warms blood above 35°C. A 40- μ m filter removes sediment from stored blood. Additionally, the system incorporates line pressure and fluid level sensors and an air detector, which minimize the chance of overtransfusion and air embolism.

An autotransfusion system salvages up to 30 to 40 per cent of red blood cell loss, thereby reducing banked blood requirements. When anticoagulated with citrate solution (6 ml per minute), washed with Plasmalyte A (1 L), and then autotransfused, scavenged blood produces satisfactory effects on coagulation, electrolyte balance, and plasma-free hemoglobin.⁵² Bacterial contamination occurs in pro-

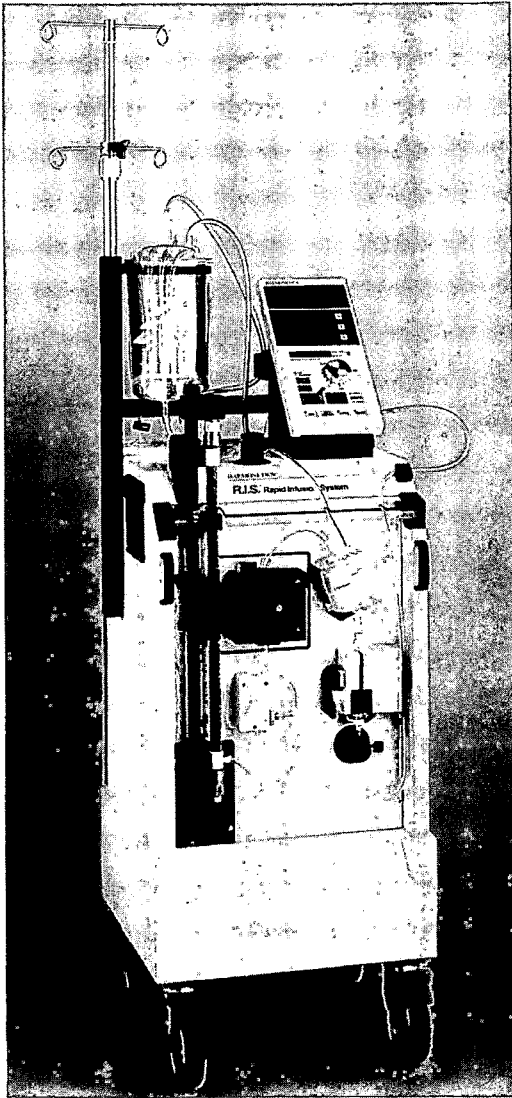


Figure 1. The rapid-infusion system designed by Sassano and manufactured by Haemonetics Inc. (Courtesy of Haemonetics Inc., Braintree, MA.)

cessed blood but is quantitatively negligible, and blood cultures are not positive after autotransfusion.⁵³ Discontinuation of autotransfusion before biliary reconstruction avoids collection of infected blood. Also, the following conditions contraindicate autotransfusion: intra-abdominal neoplasms, a positive hepatitis B antigen, and possible intraperitoneal infection, such as spontaneous bacterial peritonitis or a complicated procedure that may inadvertently enter the gastrointestinal tract.

Because of the possibility of severe coagulopathy, aggressive

Table 3. Coagulation Therapy Guided by Thrombelastographic Monitoring

-
1. Maintenance fluid
RBC: FFP: Plasmalyte A = 300:200:250 ml
 2. Replacement therapy
 - a. FFP (2 U) for prolonged reaction time ($r > 15$ min)
 - b. Platelets (10 U) for small MA (MA < 40 mm)
 - c. Cryoprecipitate (6–12 U) for persistent slow clot formation rate ($\alpha < 40^\circ$) with normal MA
 3. Pharmacologic therapy
 - a. Compare coagulability of whole blood, blood treated with protamine sulfate, and blood treated with epsilon aminocaproic acid
 - b. Epsilon aminocaproic acid (1 g) for severe fibrinolysis (F < 60 min)
 - c. Protamine sulfate (50 mg) for severe heparin effect
 - d. Heparin (1000–2000 U) for hypercoagulable state
-

monitoring and proper treatment are essential. A simple coagulation profile (prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen level, euglobulin lysis time, and fibrin degradation products) can be used but has several drawbacks. Prothrombin time depends on hepatic function and is usually prolonged in most patients. Activated partial thromboplastin time may be clinically helpful when heparin is a major cause of coagulopathy. Platelet count provides quantitative but not qualitative information. Euglobulin lysis time measures plasminogen activity but ignores antiplasmin activity. Levels of fibrin degradation products are usually positive during major surgery from reabsorption after extravascular fibrinolysis. Furthermore, a coagulation profile requires substantial time for completion. Above all, interpretation of results is difficult, because quantitative tests do not indicate the coagulability of the patient's blood.

As an alternative, thrombelastography proves to be extremely valuable for guiding coagulation therapy during liver transplantation (see Table 3).^{54, 55} It consists of a small cup containing 0.36 ml of whole blood and a freely suspended pin that is lowered into the blood specimen.¹⁰⁰ The cup is kept at 37°C and turns side by side with a 4.5° angle. When formed fibrin strands are attached on the surface of the cup and pin, the cup and pin are coupled together and the shear elasticity of the blood clot or fibrin strands is recorded on thermal paper. Therefore, thrombelastography monitors coagulability of whole blood, not quantity of coagulation factors, and assesses the entire coagulation process including coagulation and fibrinolysis. Clinically useful information is available within 30 minutes.¹²⁹

During the preanhepatic stage, dilutional coagulopathy is superimposed on coagulopathy related to insufficient coagulation factors, quantitative and qualitative defects in platelets, and fibrinolysis. Fresh frozen plasma, via the rapid-infusion system, corrects low coagulation factor levels, while a platelet transfusion remedies abnormal platelet function evidenced by a decrease in maximum amplitude in

thrombelastographic monitoring. Ten units of platelets increases platelet count by 40,000 to 50,000 μL .⁵¹ Cryoprecipitate, containing fibrinogen, factor VIII, and factor XIII, rarely becomes necessary during this period. At the onset of bypass, heparin effect is detected by thrombelastography because a small dose (1000 to 2000 U) of heparin is added in the bypass cannula. This heparin effect may last for 30 to 60 minutes and is not detectable at the end of the anhepatic stage. At this time, dilutional coagulopathy may continue, although surgical bleeding is less severe than during the preanhepatic stage.

Marked fibrinolysis can occur during the anhepatic stage, and it appears to relate to progressively increased levels of plasminogen activators, which, obviously, do not undergo hepatic clearance. However, one should reserve administration of platelets and epsilon aminocaproic acid only for severe cases of thrombocytopenia or fibrinolysis, to avoid thromboembolism in the unheparinized venovenous bypass system.

Reperfusion of the grafted liver often induces severe coagulopathy for several reasons: (1) dilutional coagulopathy from influx of preservation solution, (2) release of heparin or heparin-like substance from donor hepatocytes, (3) explosive fibrinolysis by the release of plasminogen activator from the donor liver, and (4) inhibition of coagulation by unknown substances.⁴⁵ The anesthesiologist differentiates the cause of this pathologic event by comparing thrombelastography of whole blood, blood treated with protamine sulfate, and blood treated with epsilon aminocaproic acid (Fig. 2).⁵⁵ Protamine sulfate, 50 mg intravenously, effectively reverses persistent heparin effect (that is, 30 minutes after reperfusion), whereas a single 1-g dose of epsilon aminocaproic acid treats severe fibrinolysis (fibrinolysis time <60 minutes). It is controversial whether fibrinolysis is primary or

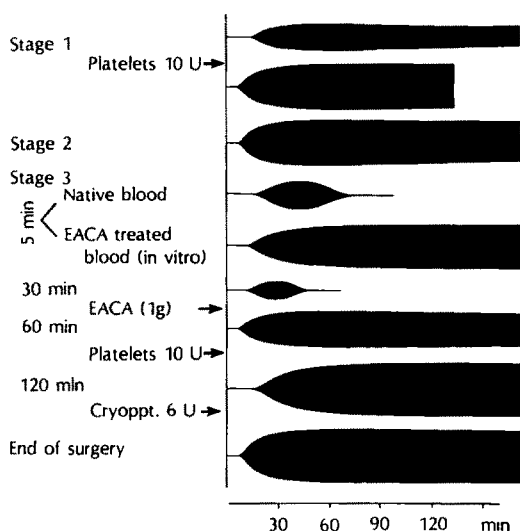


Figure 2. Thrombelastographic monitoring, replacement therapy, and pharmacologic therapy in a liver transplant recipient. (From Kang Y, Gelman S: Liver transplantation. In Gelman S (ed): *Anesthesia and Organ Transplantation*. Philadelphia, Saunders, 1987, p 173; with permission.)

secondary to disseminated intravascular coagulation. However, the primary theory is gaining more support owing to the association of fibrinolysis with an isolated decrease in fibrinogen and factors V and VIII,⁷¹ fulminant increases in plasminogen activator levels,⁹⁶ and the success of epsilon aminocaproic acid without thrombotic complications.⁵⁵ Severe coagulopathy improves gradually during the neohepatic stage unless major surgical bleeding occurs or the grafted liver functions inadequately.

A hypercoagulable state sometimes occurs in patients with hepatic neoplasms or the Budd-Chiari syndrome. During surgical bleeding, this abnormality may normalize or blood may actually become hypocoagulable. However, when surgical bleeding is minimal, administration of a small dose of heparin (1000 to 2000 U IV) should be considered during veno-venous bypass.

Renal Function, Electrolytes, and Acid-Base Balance. Adequate urine output should be maintained because hemolysis occurs after multiple blood transfusions and cyclosporine impairs renal function postoperatively. During surgery, persistent oliguria is troublesome. Following clamping of the IVC, renal venous congestion and hematuria frequently occur, resolving slowly at the end of surgery.¹⁰⁸ The simple cross-clamping technique appears not to increase the incidence of postoperative renal dysfunction or hemodialysis,¹²² but a controlled, comparative study is needed. Polson and coworkers⁹⁵ note better postoperative renal function in patients who receive mannitol and an infusion of low-dose dopamine (2 to 3 μ g per kg per minute), although they studied a small patient population.

Preoperative hyponatremia and hypokalemia become corrected during surgery; sodium and potassium are maintained within the normal range by the large volumes of fresh frozen plasma and balanced electrolyte solution. However, repeated doses of sodium bicarbonate, given for severe metabolic acidosis, may cause hypernatremia. Progressive hyperkalemia may result from inadequate renal function and the large volumes of rapidly transfused banked blood. Aggressive management is necessary to avoid lethal hyperkalemia on reperfusion. Glucose and insulin treats moderate hyperkalemia (4.5 to 5.5 mEq per L), although its effectiveness is unknown in those with insulin resistance. The use of washed red cells largely prevents hyperkalemia.¹⁰ When progressive hyperkalemia occurs, we use the autotransfusion system to wash and return phlebotomized blood or to wash banked red blood cells before transfusion. Severe hyperkalemia (7 to 10 mEq per L) can occur on reperfusion of the grafted liver, leading to tall, peaked T-waves on the ECG and gradual bradycardia including sinus arrest.¹⁴ Intravenous calcium chloride and sodium bicarbonate provide symptomatic therapy. During the neohepatic stage, potassium levels decrease gradually owing to hepatic reuptake of potassium.¹ Potassium supplementation must be judicious, because overzealous correction will potentiate hyperkalemia in case of postoperative renal dysfunction or a poorly functioning liver.

During the preanhepatic stage, ionized calcium levels decrease

gradually as serum citrate values progressively approach the values contained in banked blood. Maximal changes occur during the anhepatic stage, and then citrate levels decrease 60 minutes after reperfusion.⁸⁴ Therefore, severe ionized hypocalcemia (<0.6 mmol per L) is unavoidable during the anhepatic stage or during massive blood transfusions, and can produce myocardial depression when serum Ca^{2+} falls below 0.56 mmol per L. This mandates frequent measurement and normalization of Ca^{2+} with CaCl_2 because calcium gluconate requires hepatic metabolism to liberate Ca^{2+} . However, a recent study⁸² shows that equimolar doses of CaCl_2 and calcium gluconate equally correct ionized hypocalcemia in patients undergoing liver transplantation.

Progressive metabolic acidosis and an increase in lactate levels, particularly during the anhepatic stage, result from deficient hepatic clearance of acidic substances. Reperfusion of the grafted liver brings forth severe metabolic acidosis and increased lactate levels owing to absorption of metabolic acids from the ischemic donor liver. Persistent acidosis occurs in patients with unstable cardiovascular function and a poorly functioning liver. Because severe acidosis impairs myocardial function and tissue respiration, we give sodium bicarbonate to maintain a base deficit less than 5, particularly right before and after reperfusion. Base deficit decreases gradually in most patients, and metabolic alkalosis occurs in some by the end of surgery. Although sodium bicarbonate therapy may promulgate hyponatremia, hyperosmolality, and postoperative alkalemia, these conditions are relatively benign compared with the possible hemodynamic consequences induced by severe metabolic acidosis.

In a recent study,³⁸ postoperative metabolic alkalosis did not relate to the volume of blood given intraoperatively or the dose of sodium bicarbonate. Furthermore, 70 per cent of patients with postoperative metabolic alkalosis survived, whereas all patients with metabolic acidosis died. Therefore, late intraoperative and postoperative metabolic alkalosis appears to be the natural course of those surviving liver transplantation and occurs secondary to steroid therapy, drainage of gastric content, and hormonal interaction.

Anesthesia for Retransplantation

Retransplantation rates vary from institution to institution, but the overall incidence falls below 15 per cent in adults. Retransplantation may be required within a few days for patients who inadvertently receive a poorly functioning donor liver, suffer vascular complications (for example, hepatic arterial or portal venous thrombosis), or develop hyperacute rejection. Obviously, these patients have many problems, such as acute respiratory distress syndrome or severe metabolic acidosis, and they require supportive therapy. When severe liver necrosis develops, early removal minimizes toxic effects of the dying liver. In these patients, retransplantation is relatively simple, because all dissections have already been performed.

A second group of patients require retransplantation several

weeks or months after the first surgery because of chronic rejection or vascular complications. Their physical condition has improved but may be complicated by cyclosporine-induced hypertension and renal insufficiency. The operation often proves very difficult because of adhesions and fragile tissue secondary to prolonged steroid administration.

Pediatric Cases

Details of anesthetic management of pediatric liver transplantation can be found in several review articles.¹⁴ Patients with cholestatic disease (biliary atresia) and inborn errors of metabolism receive liver transplants, although all types of disease can be an indication for surgery. Pulmonary arterial catheterization does not appear necessary in all pediatric patients because of their relatively healthy myocardium, and access may be difficult. Multiple intravenous catheters are inserted according to the size of the patient, and a cutdown of the internal jugular vein may be required for central venous cannulation. Although blood transfusion requirements are proportional to those in the adult, a rapid-infusion system may not be necessary because of smaller total transfusion volumes. Children appear to tolerate cross clamping of major vessels with less hemodynamic instability. Currently, the veno-venous bypass system is used only for children weighing more than 20 kg, mainly due to the difficulties in achieving safe minimal bypass flows in small children. In comparison with adults, the intraoperative course, occurrence of postreperfusion syndrome, and intraoperative coagulopathy are similar. However, coagulation problems occur to a lesser degree, because cholestatic disease is more prevalent in children.⁵⁶ It is interesting to note that children tend to develop hypertension and metabolic alkalosis earlier than adult recipients.

Conclusion of Anesthesia

At the conclusion of surgery, recipients are transported to the intensive care unit without reversal of muscle relaxation. Their ECG and blood pressure are monitored in transit. Upon arrival at the intensive care unit, all hemodynamic monitoring is resumed and the patient receives mechanical ventilation (5 cm H₂O PEEP and Fio₂ 50 to 70 per cent). Recipients are allowed to recover from anesthetic agents and muscle relaxants, and the immediate postoperative care is similar to that of other patients after major surgery. Details of medical and surgical postoperative care may be found in review articles.^{105, 124}

SUMMARY

Liver transplantation has allowed 70 per cent of patients who otherwise had no chance of survival to survive at least 1 year, and

more than 50 per cent of them currently survive longer than 5 years. The technology, methods, and knowledge resulting from liver transplantation have made a remarkable contribution to medicine. Future investigation by anesthesiologists in this field will not only help patients with and without liver disease, but also improve our understanding of hepatic physiology and its relation to anesthesia practice.

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Anesthesia for Adrenal-Caudate Transplant

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Parkinsonism is a striatal dopamine-deficiency syndrome characterized by tremor, rigidity, and bradykinesia. Surgical ablation of central nervous system (CNS) structures ameliorates tremor, but the improvement is not long-term. Since 1967, the mainstay of therapy has been levodopa, which increases dopamine levels in the brain.

A new surgical procedure, involving transplantation of autologous adrenal medulla into the basal ganglia to resupply the ganglia with a continuous source of dopamine, has been described.^{2, 43} We have anesthetized 18 patients with refractory parkinsonism for adrenal-caudate transplants. Initial results have been encouraging, but the long-term efficacy of this procedure for a permanent cure of parkinsonian symptoms is unknown.

This article discusses the pathophysiology of parkinsonism and its pharmacologic management as they relate to the problems of anesthetic management of patients undergoing adrenal-caudate transplant.

HISTORY OF PARKINSONISM

Parkinsonism is a rare disease, with an incidence of 18.2 per 100,000 population (excluding drug-induced cases). Ninety per cent of untreated patients die within 15 years. Primary parkinsonism accounts for 85 per cent of all cases.⁶⁵

In 1817, James Parkinson published a small monograph entitled *An Essay on the Shaking Palsy*.⁵⁵ This monograph contains the observations of only six patients. Parkinson treated only two; he observed the others only casually. He notes the onset of tremor in one limb. The tremor spreads within a year. Movements become slower and posture becomes stooped. Gait disturbances, including short shuffling

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steps, worsen until walking is impossible. Eventually, the patient becomes totally bedridden and helpless. Later investigators wrote about Parkinson's disease but made little improvement on Parkinson's original description.

After Parkinson's monograph, the pathophysiology of the disease remained a mystery for a century and a half. In the early twentieth century, encephalitis lethargica (von Economo's disease, sleeping sickness) underwent a worldwide epidemic. Fifty per cent of affected patients subsequently developed symptoms²⁰ similar to parkinsonism. After the epidemic passed, new cases of parkinsonism again became rare.

In 1954, Rauwolfia alkaloids (reserpine) were introduced to treat hypertension.^{19, 38} Reports of parkinsonism associated with reserpine¹⁷ emerged soon after its introduction. Reserpine depletes 3-hydroxy tyramine (dopamine) levels in the brains of rabbits.¹³ The animals become sedated and develop ptosis.¹² Symptoms promptly resolve after administration of 3,4-dihydroxyphenylalanine (DOPA). These findings prompted investigators to question previously held concepts about dopamine. Dopamine, they thought, was only an inactive precursor of norepinephrine, which had no other systemic effects.

The link between dopamine and parkinsonism came a few years later. Hornykiewicz and coworkers²¹ noted that the substantia nigra was pale in primary and postencephalitic parkinson patients. They also found low dopamine concentrations in these patients. Soon thereafter, scientists found that dopamine could be replaced by exogenous racemic DOPA, and that the compound,¹⁶ specifically levodopa,¹⁵ improved most symptoms of parkinsonism. Since 1967, levodopa therapy has been the standard of care for parkinson treatment.

CLASSIFICATION OF PARKINSONISM

Parkinsonism is classified according to etiology: primary (Parkinson's disease), secondary, and "parkinsonism-plus."

Primary parkinsonism usually develops in the fifth to sixth decade of life. It is neither infectious nor hereditary.²⁰

Secondary parkinsonism follows infection or environmental toxins. It may occur after encephalitis, brain tumors, carbon monoxide poisoning,²⁰ boxing,²⁹ and drug exposure. Drug-induced parkinsonism is the most common form of secondary parkinsonism.⁵⁷

Parkinsonism also occurs as a symptom of multiple organ system dysfunction. It occurs with normal pressure hydrocephalus,⁴⁶ Alzheimer's disease,²⁵ Wilson's disease,⁴⁴ Huntington's disease,⁴⁹ and autonomic dysfunction (Shy-Drager syndrome).⁶²

STAGING OF PARKINSONISM

Hoehn and Yahr³³ developed a five-stage classification system for evaluating disability from parkinsonism (Table 1). Minimal, unilateral

Table 1. *Parkinsonism Disability Scale*

CLASS	SYMPTOMS
Stage I	Unilateral involvement
Stage II	Minimal or no impairment
Stage II	Bilateral or midline involvement
Stage III	No impairment of balance
Stage III	Impairment of righting reflex
Stage III	Activities somewhat restricted
Stage III	Independent functioning
Stage III	Mild to moderate disability
Stage IV	Fully developed severe disease
Stage IV	Walks and stands unassisted
Stage IV	Markedly incapacitated
Stage V	Confined to bed or wheelchair

involvement represents stage I, whereas confinement to bed or a wheelchair characterizes stage V. This system was described before the widespread use of levodopa, so it reflects the course of untreated parkinsonism. Other schemes, such as the Columbia University rating scale or Webster rating scale,²⁶ help to quantify effectiveness of therapy.

DRUG TREATMENT

Levodopa

Because dopamine does not cross the blood brain barrier when administered systemically, it has no therapeutic effect in parkinsonism. Levodopa (Fig. 1), the immediate precursor of dopamine, does permeate striatal tissue where it is decarboxylated to dopamine by aromatic l-amino acid decarboxylase. The coenzyme pyridoxine enhances the activity of aromatic l-amino acid decarboxylase, which is present in the CNS and peripheral tissues.⁵⁶ The wide distribution of aromatic l-amino acid decarboxylase may result in low levels of CNS dopamine and, thus, poor control of symptoms. Increasing the dosage of levodopa enhances side effects such as orthostatic hypotension, arrhythmia, anorexia, nausea, vomiting, and dyskinesias.

Blocking peripheral activity of aromatic l-amino acid decarboxylase with carbidopa or benzserazide (Fig. 1) causes more levodopa to penetrate the CNS before conversion to dopamine. Therefore, therapeutic effects are achieved with fewer side effects. Carbidopa and benzserazide are effective because they minimally cross the blood brain barrier and act peripherally.

For all its benefits, levodopa does not change the course of parkinsonism. Efficacy decreases with increased duration of therapy.²³ Mortality occurs at a rate similar to the normal population for the first 6 years of therapy but appears to increase after that.⁵⁷ During therapy,

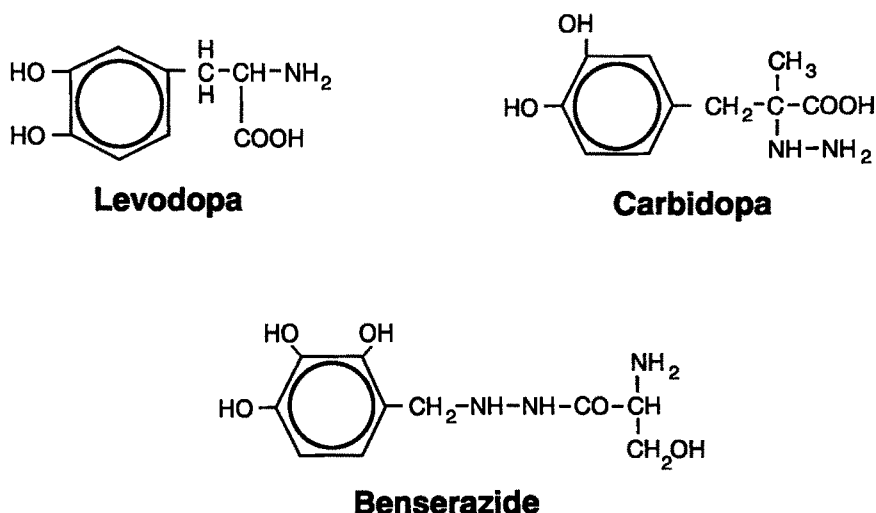


Figure 1. Chemical structures for levodopa, carbidopa, and benzserazide.

an “on-off” phenomenon is characterized by periods of poor control (off phase) interrupting periods of good control (on phase). The on-off phenomenon becomes more likely with longer duration of therapy and higher doses.¹ Off periods occur abruptly in at least 10 per cent of patients. Increased doses of levodopa will not control this phenomenon. These periods may improve with the use of aromatic L-amino acid decarboxylase inhibitors or “drug holidays.”^{56, 65} In comparison to the on-off phenomenon, the “wearing off” phenomenon, which occurs when plasma concentrations fall too low, responds to levodopa administration.

Adjunctive Drugs

Drugs with dopaminergic activity may be useful in the management of parkinsonism. Amantadine,⁶¹ originally marketed as an antiviral agent, and bromocriptine,^{54, 61} an ergot alkaloid, increase dopamine stimulation. The mechanism of action is not clear but may involve increased release of dopamine or stimulation of dopamine receptors. These agents are used in patients who are refractory to levodopa.

Monoamine oxidase inhibitors (MAOI) increase catecholamine levels by preventing breakdown. Certain MAOIs selectively inhibit dopamine metabolism, including (–)deprenyl and (+)trancylpromine. They do not induce the severe hypertension known to occur following administration of phenelzine or iproniazid.⁶⁵

Cholinergic Drugs

Coordinated muscle movements are thought to result from a balance between dopaminergic and cholinergic stimulation.^{1, 4} When

central dopaminergic stimulation fails to improve parkinsonian symptoms, some patients experience improvement by pharmaceuticals that block central cholinergic stimulation. Anticholinergic drugs such as trihexyphenidyl and benztropine are useful. However, large doses slow gastric emptying and may decrease absorption of levodopa.⁴ Older patients may experience hallucinations, psychoses, and other CNS aberrations.⁶⁵ Antihistamines, such as diphenhydramine, have weak central anticholinergic effects; side effects are less severe. Thus, they may be better tolerated by older individuals.

SURGICAL INTERVENTION

Past

In 1939, investigators²⁰ first excised parts of the brain or spinal cord for parkinsonism. The dismal results of these operations led to their abandonment.

Other operations developed from Parkinson's original monograph. He noted that one patient's tremor resolved for 2 weeks after he suffered a stroke.²⁰ In 1952, Cooper¹⁴ found that unilateral resting tremor disappeared after occlusion of the anterior choroidal artery. Unfortunately, this treatment did not produce long-term benefit. Stereotactic basal ganglia lesions transiently improved symptoms¹⁴ but also lacked sustained effectiveness.

Following the introduction of levodopa, surgical treatment has been uncommon, because these operations do nothing to alter the course of the disease. They are now reserved for the most refractory tremors.

Present

Different forms of therapy are necessary to help patients who are refractory to current pharmacologic and surgical methods and, thus, are at the outer limits of the disease. Unlike old methods, new methods should accomplish more than a decrease in symptoms. New therapies should seek to increase striatal dopamine levels and to correct basal ganglia degeneration.

In rats with substantia nigra lesions, transplantation of healthy substantia nigra partially re-innervates this structure and improves behavior.⁶ Other studies show similar improvement after transplanting autologous adrenal medulla to the basal ganglia.³¹ Medulla cells also have the capability of re-innervating brain tissue.⁵³

In 1985² and then in 1987,⁴³ several groups of investigators reported on the first human trials of autologous adrenal medulla to caudate nucleus transplants. They reported on small numbers of patients and had short follow-up periods. Nevertheless, the results have encouraged controlled trials and long-term follow-up studies.

Table 2. *A Recommended Anesthetic Technique*

Frame placement	Sedation with midazolam Local anesthesia: 1% lidocaine with epinephrine and 0.5% bupivacaine mixture (10–15 ml)
Tracheal intubation	Additional midazolam in 1-mg increments Topical airway anesthesia: nebulized 4% lidocaine (4–5 ml); viscous 2% lidocaine (15 ml nasally) 0.5% phenylephrine nasal spray Insert warmed nasotracheal tube Fiberoptic intubation
Induction	Thiopental, 3–5 mg/kg Sufentanil, 0.5–1 µg/kg Vecuronium, 100 µg/kg
Maintenance	Sufentanil infusion, ≥ 0.3 µg/kg/hr (range 0.26–0.48 µg/kg/hr) Vecuronium infusion, ≥ 1 µg/kg/min (range 0.18–1.4 µg/kg/min) 66% nitrous oxide in oxygen
Reversal	Isoflurane, 0.3–0.5% end tidal Neostigmine, 50 µg/kg Glycopyrrolate, 10 µg/kg Naloxone, titrate to effect

METHODS FOR ADRENAL-CAUDATE TRANSPLANT

To begin the procedure, the neurosurgeon places a stereotactic head frame under local anesthesia. After stereotactic identification of the lateral ventricle and right caudate nucleus, the patient is transported to the operating room. In our center, patients are sedated with midazolam and the airway is anesthetized with topical lidocaine (Table 2). We intubate the trachea transnasally, using a fiberoptic bronchoscope, then induce general anesthesia with thiopental, and maintain it with a balanced anesthetic technique (Table 2).

The patient is placed in the left lateral decubitus position, with the head rotated to the right. The surgeon performs a right adrenalectomy through a flank incision. The neurosurgeon places an Ommaya reservoir for postoperative sampling of cerebrospinal fluid (CSF) and then proceeds with craniotomy to expose the right caudate nucleus through a transcortical incision. After the adrenalectomy, the medulla is separated and fragmented. The fragments are placed in a "pouch" in the caudate nucleus. The wounds are closed and the anesthetic discontinued. Extubation of the trachea occurs in the operating room so that reintubation, if necessary, can be accomplished with optimum facilities and assistance.

PERIOPERATIVE CONSIDERATIONS IN PARKINSONISM

Before widespread use of levodopa, the most common nonsurgical postoperative complication was bronchopneumonia, which most

likely resulted from immobility in this impaired group of patients.³³ Postoperative mobility can be facilitated by adequate preoperative therapy of muscle symptoms. The patient with dysphagia and impaired coughing ability more likely aspirates saliva or gastric juice than one with well-controlled parkinsonism.⁷ In our series of 18 patients, the first two did not receive levodopa the morning of operation, and they required levodopa for "wearing off" in the recovery room.

The half-life of levodopa is short (1 to 3 hours).⁵ Withholding a dose for 6 hours may allow the plasma level to fall by 75 per cent or more. Therefore, "wearing off" may occur by the end of a long operation. Recommendations to stop levodopa for 6 to 12 hours preoperatively²⁷ are based on the possibility of arrhythmia and hypotension. Arrhythmia is possible²⁷ but is not a significant consideration. None of our patients experienced arrhythmia after receiving levodopa on the morning of surgery.

Hypotension may be caused by dopamine-induced depletion of peripheral and cardiac norepinephrine stores.^{42, 50} However, hypotension sometimes occurs in patients with Parkinson's disease who have never received dopamine,⁹ confusing the issue of whether levodopa per se actually causes perioperative hypotension.

In our series, arterial blood pressure remained within 30 per cent of baseline in most patients. During surgery, hypertension responded promptly to increasing anesthetic depth. Norepinephrine levels remained significantly below baseline throughout the procedure (Fig. 2), which may have resulted from anesthetic effect.²⁴ During adrenal manipulation, epinephrine levels increased substantially above baseline (Fig. 3). Interestingly, blood pressure changes did not correlate with changes in epinephrine or other catecholamines.³⁵

On the basis of our results, we recommend continuing antiparkinson therapy into the immediate preoperative period. Our last 16 patients received levodopa up until the time of operation. None experienced "wearing off" in the recovery room.

Stereotactic Procedures

Stereotaxis is a procedure for localizing intracranial targets. The targets are assigned three-dimensional coordinates relative to a head frame; a computed tomography (CT) scan provides target point identification. A biopsy of tumors or drainage of abscesses is frequently possible through a burr hole. Stereotaxis may also enhance formal craniotomy if a lesion is difficult to locate.

We use a Brown-Roberts-Wells (BRW) stereotactic system.^{30, 60} The BRW system consists of a base ring and a frame (Fig. 4). The ring attaches to the skull and the frame attaches to the ring. Of importance is that the ring lies in front of the nose and mouth and prevents easy airway access.

Stereotactic procedures are possible with local anesthesia and intravenous supplementation. This is well tolerated by most patients. In those considered to be poor candidates for local anesthesia, however, induction of general anesthesia should occur before frame place-

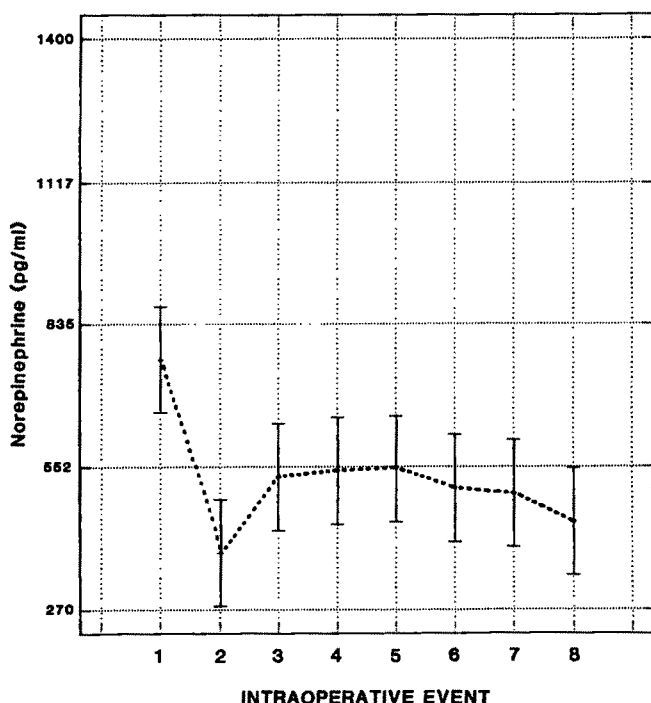


Figure 2. Change in plasma norepinephrine (mean $\pm$ SD) during intraoperative period (n = 6). The events are (1) baseline, (2) after induction, (3) during adrenal dissection, (4) after adrenal dissection while waiting for caudate preparation, (5) adrenal manipulation, (6) adrenal vein ligation, (7) placing the graft, and (8) closing. The levels are significantly higher at baseline than at any time intraoperatively.

ment. Intubation of the trachea can proceed normally without the frame in place. This usually occurs in the radiology department. After CT, the patient is transported to the operating room under anesthesia.

We greatly prefer the patient to be awake for fiberoptic intubation in the operating room after CT.³⁵ This method avoids problems associated with transporting anesthetized patients through elevators and corridors. Sedation with a benzodiazepine increases patient acceptance and limits hemodynamic responses.⁶⁸

Anesthetic Drugs

Intravenous Agents. Perianesthetic drugs should lack adverse interactions with parkinson symptoms or therapy. Agents commonly used for induction and premedication may be unacceptable in parkinsonism.

Barbiturates seem to have no interaction with the disease or antiparkinson drugs but may aggravate hypotension. Ketamine may im-

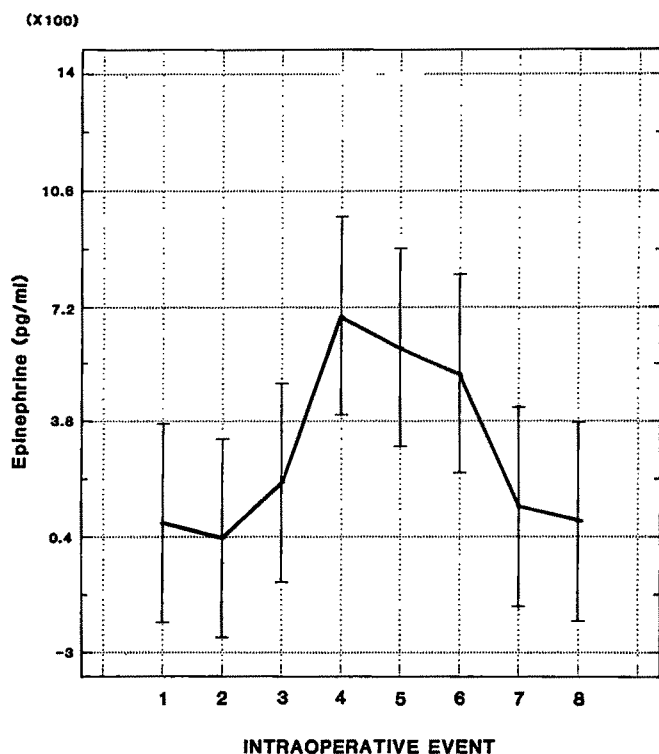


Figure 3. Change in plasma epinephrine (mean $\pm$ SD) during intraoperative events ($n = 6$). The events are (1) baseline, (2) after induction, (3) during adrenal dissection, (4) after adrenal dissection while waiting for caudate preparation, (5) adrenal manipulation, (6) adrenal vein ligation, (7) placing the graft, and (8) closing. The levels during adrenal manipulation are significantly higher than baseline.

prove dyskinesias.³² Etomidate may cause athetoid movements, yet these movements should be distinguishable from tardive dyskinesias. However, the drug should be used cautiously.

Benzodiazepines are probably acceptable,⁵⁶ although high doses of diazepam (100 mg per day) may cause parkinson-like symptoms.⁶⁷ Several authors postulate that this finding relates to GABA-mediated dopamine inhibition⁶⁷ or to some interference with endogenous opioid.⁵⁹

Narcotics are also acceptable for use in patients with parkinsonism. Brindle⁷ suggested that the anesthesia team should avoid fentanyl because of the possibility of muscle rigidity. We have used sufentanil infusion in all patients, and have not found this to be a problem.

Phenothiazines and butyrophenones are central dopamine antagonists⁵⁶ and may cause tardive dyskinesias. Droperidol, a butyrophenone used in neuroleptanesthesia, has been used in parkin-

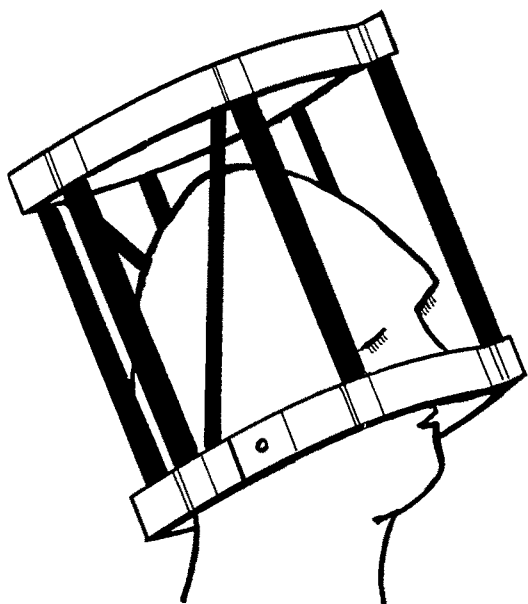


Figure 4. Head frame used for the procedure at Vanderbilt.

sonism without complications.⁵² Even in small doses,⁴⁵ it may cause tardive dyskinesias in otherwise healthy patients.⁵⁸ Droperidol also prevents re-uptake of norepinephrine by the adrenal medulla and could aggravate hypertension during adrenalectomy.⁶⁶

Metoclopramide may cause dyskinesias and parkinsonism.⁴⁰ The mechanism is not clear, but it may involve mechanisms independent of the striatonigral system.⁶⁹ It also decreases intestinal absorption of levodopa.⁶³

Volatile Agents. Volatile anesthetics are useful for adrenal caudate transplant. There are no reports of altered sensitivity in parkinsonian patients to any halogenated agent. We employ them to control blood pressure during balanced anesthesia, but they may also be used as the primary anesthetic. Volatile anesthetics should not cause or worsen hypertension or arrhythmia. Goldberg²⁷ recommends the avoidance of cyclopropane or halothane in parkinsonian patients on levodopa therapy because he has concerns about the possibility of arrhythmias. There are, however, no actual reports of problems with these or any other volatile agents.

Adrenalectomy causes transient increases in plasma epinephrine levels. Epinephrine-induced arrhythmias occur at lower concentrations with halothane,³⁷ so isoflurane or enflurane appear to be better choices.

Nitrous oxide can produce alpha-receptor stimulation,⁶⁴ possibly leading to increased systemic vascular resistance. However, this effect alters blood pressure insubstantially, because nitrous oxide also

causes myocardial depression. Parkinsonism does not contraindicate the use of nitrous oxide.

Muscle Relaxants. The use of muscle relaxants largely depends on personal preference and individual patient requirements. Characteristics of individual relaxants will influence the decision of which relaxant to use.

Succinylcholine reportedly causes hyperkalemia in parkinson patients.²⁸ However, this finding is based on experience with a single parkinson patient, who received 800 mg in 30 minutes. Clark⁸ found that parkinson patients respond normally to doses of D-tubocurarine. No data exist to the contrary for other nondepolarizing relaxants.

Muscle relaxants may alter sympathetic function. For example, pancuronium is vagolytic⁴⁸ and sympathomimetic.¹⁸ Exaggerated sympathetic responses have followed use of pancuronium during adrenal manipulation in pheochromocytoma.³⁹ When given in larger therapeutic doses, atracurium, metocurine, and D-tubocurarine stimulate histamine release. Increased histamine levels usually cause hypotension but, at the same time, may cause the release of catecholamines.³⁴

We prefer to use a vecuronium infusion in these patients. This nondepolarizing agent does not alter hemodynamic stability^{47, 48} in usual clinical doses, nor does it produce significant release of histamine in low doses³ or even higher doses.¹¹ There is no accumulation.⁵¹ Normal patients require infusion rates of about 1 μ g per kg per minute to maintain twitch height at 10 per cent of control.¹⁰ Parkinson patients require about the same rate of infusion (0.67 ± 0.11 μ g per kg per minute).³⁵

Differentiating postoperative parkinsonism from residual blockade may be difficult. Therefore, accurate monitoring of blockade with a nerve stimulator is essential. Visual assessment of train-of-four⁴¹ is adequate but potentially unreliable. Detection of fade may be difficult when train-of-four ratio exceeds 0.4.^{36, 70} Assessment of other criteria for recovery (for example, hand grip and head lift) increases the reliability of this method. However, parkinson patients may be unable to perform these tests, so assessment of residual blockade may be unreliable.

A more reliable method of monitoring is a recording blockade monitor. This permits accurate determination of recovery and fade. We have used both evoked electromyography (EEMG) and linear force transducer in our group with parkinsonism patients. Both devices allow accurate assessment of evoked response and recovery to prere relaxant levels. No patient exhibited residual blockade or recurarization after reaching 100 per cent recovery (control levels). These devices are available at moderate cost. The force transducer is more troublesome because it must be firmly affixed to the table and not moved after baseline measurements. These devices are not mandatory, but resolve a potential dilemma at the end of the operation.

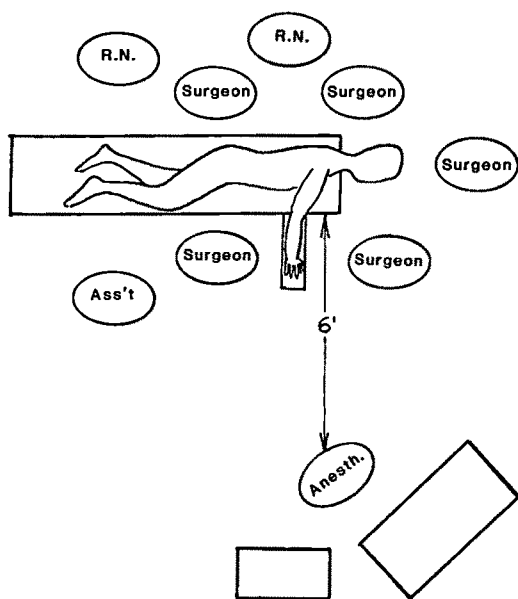


Figure 5. Operating room setup for adrenal caudate transplant.

Arrangement of the Room

Because there are two operations performed simultaneously, many people are involved in the case. Eight surgeons and nurses must stand around the patient, causing limited work space. Figure 5 suggests a useful floor plan. Other arrangements are possible, but this one seems to provide adequate space for surgical personnel and equipment. The anesthesiologist, unfortunately, has limited access to the patient. At the closest point, he is about 5 feet from the patient.

This distance is possible because of long anesthesia circuits and a recording nerve stimulator. Long connections on all monitors minimize the need to be closer to the patient.

Perioperative Complications

In our series of 18 patients who had an adrenal-caudate transplant, surgical complications included pneumothorax (three patients), abscess (1 patient), and retroperitoneal bleeding (1 patient). There were no immediate perioperative deaths. One patient died of an unrelated myocardial infarction several months postoperatively. None of the patients required ventilation in the immediate postoperative period. One patient with stage V involvement developed adult respiratory distress syndrome 2 weeks after surgery. Dysphagia and immobility probably contributed to the pulmonary problem.

In general, the patients have been sleepier on emergence than would be expected with our anesthetic technique (see Table 2). This may result from residual anesthetic, benzodiazepine, or the parkinsonism. Phenytoin, given preoperatively for seizure prophylaxis,

could contribute to this somnolence. To date, we have not encountered significant problems with these patients in the recovery room. The following approach has provided satisfactory analgesia: (1) transcutaneous electrical nerve stimulator unit placed on the flank incision, and (2) small doses of codeine (7.5 to 30 mg) intravenously as needed. Patients receive a nasogastric tube prophylactically and at present none have been nauseated in the recovery ward. For nausea, diphenhydramine is preferred, because it is not a dopamine antagonist.

FUTURE OF ADRENAL-CAUDATE TRANSPLANT

It is too early to comment on the long-range results of this operation. At this time, about half of the patients have experienced a beneficial effect: improved balance, less bradykinesia, and fewer gait abnormalities. Furthermore, none of the surviving patients are worse after the operation (G. S. Allen, MD, personal communication).

Postmortem examination on the patient who died of myocardial infarction showed probable survival of the transplanted cells. It remains unclear whether the transplant of these cells actually contributes to improvement of symptoms. It may be that the procedure represents merely another method of creating lesions in the basal ganglia and that improvement will not be long-term. Sufficient time for long-term follow-up is required to determine the true efficacy of the method.

Other possible applications exist for adrenal caudate transplant. Huntington's disease is another degenerative disease of the cholinergic neurons in the basal ganglia. Some data suggest that adrenal caudate transplant may be effective in this disease as well (N. B. Tulipan, MD, unpublished data).

SUMMARY

We have given anesthesia for 18 adrenal-caudate transplants. A controlled trial of 200 patients is anticipated at our center. If this procedure proves to have long-term benefit, it will certainly be performed outside of research centers. To provide optimum services, members of the anesthesia team must understand the basic principles of preoperative management in patients with parkinsonism. Specifically, they need to be familiar with possible interactions that may alter the choice of drugs in the perianesthetic period. Additionally, some of the logistical problems, such as airway availability during stereotaxis and large numbers of people in the operating room, need to be remembered. Our series is instructive for future operations, as well as for the management of the individual with Parkinson's disease, who has anesthesia for a different surgical procedure.

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Laser Therapy for Bronchoscopy

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The principles of lasers originated in the quantum optical theories of Einstein¹⁴ in 1917; however, 41 years elapsed before Schawlow and Townes⁵¹ won the Nobel Prize for experiments based on these theories. In 1960, Maiman²⁸ described stimulated optical radiation in ruby using energy from a high-powered flash lamp to produce a population of chromium ions in the metastable state. This was the first laser constructed in the United States. Studies of the surgical applications of laser beams were presented by McGuff³⁶ and Malt³⁰ in 1964. The first use of lasers during bronchoscopy was presented by Strong and associates⁵⁸ using the CO₂ laser. Patients selected by Strong's group had inoperable, symptomatic, and obstructive lesions of the trachea and mainstem bronchi. Since these early reports, many authors have presented their series describing the beneficial results in these patients, who previously were offered no effective therapeutic modality.^{13, 32, 35, 46}

In this article, the clinical features of patients selected for bronchoscopic laser treatments, and the surgical and anesthetic considerations are discussed. Elsewhere in this edition, Dr. McLeskey has described the physics of lasers.

ANATOMIC AND PATHOPHYSIOLOGIC CONSIDERATIONS

Any area below the vocal cords that can be visualized with a bronchoscope is amenable to laser therapy. The CO₂ laser has a wavelength of 10.6 μm and travels in a straight line; therefore, its use is, for the most part, confined to lesions that can be seen directly with the rigid bronchoscope. The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, however, has a wavelength of 1.06 μm and can be transmitted through flexible quartz fibers. Therefore, lesions that can be visualized with the flexible fiberoptic bronchoscope (that is, in the lobar and segmental bronchi) can be treated with this laser.^{24, 56} Over-tight-

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ening of the flexion cable allows flexion of 180 degrees with the laser quartz light guide in place. Thus, even lesions in the upper lobe bronchi that are difficult to visualize can now be effectively treated with the Nd:YAG laser.

Pathology

Virtually any type of lesion in the tracheobronchial tree can be treated with the laser. Cancer tissue is more susceptible than normal tissue to laser-induced destruction, and this unique oncolytic feature was described by Minton and Ketcham.⁴⁰ When the laser beam hits the malignant tissue, temperatures instantly reach 100 degrees C, causing destruction of cellular elements and denaturation of proteins. Squamous cell carcinomas are most commonly encountered and treated; however, metastatic lesions respond as well.³⁵ Most bronchoscopists use the criteria of McDougal and Cortese³¹ when selecting cancer patients for laser treatments: the lesion should protrude into the bronchial wall without obvious extension beyond the cartilage, and the axial length of the lesion should be less than 4 cm. Low-grade malignant tumors, such as carcinoid lesions, should not be treated with lasers if they are resectable, because bleeding is significant and complete excision with the laser is not feasible.⁴⁶

The granulation tissue and tracheal webs that form at the site of previous tracheostomies or endotracheal tube cuffs can cause significant airway obstruction. These tissues respond favorably to laser treatment unless there is distortion and destruction of the cartilage. In such cases, the beneficial effects of laser treatments are temporary, and these lesions are managed best by resection with tracheal reconstruction.³⁵

Recurrent respiratory papillomatosis is most common in childhood but occurs at all ages and is a therapeutic challenge to all otolaryngologists. These benign tumors are both laryngeal and tracheal in origin, occurring in the epithelial layer of the upper respiratory system and often producing symptoms of airway obstruction. Laser bronchoscopy is the most effective means of treating these lesions⁵⁶; however, recurrence is the norm. Several patients, who have contracted this disorder secondary to a viral illness²³ have required multiple general anesthetics and laser bronchoscopic treatments.

Other lesions that have been successfully treated with laser bronchoscopy include lipomas, hamartochondromas, schwannomas, histiocytofibromas, sclerosing hemangioma, squamous metaplasia, and amyloid tumors.⁴⁷

Clinical Presentation

Children who present for laser bronchoscopy range from a few months old to adolescence and usually have a diagnosis of papillomatosis. The lesions usually start in the larynx, and tracheostomies are often performed to relieve airway obstruction. The spread of the lesions to the trachea seems to be related to the tracheostomies as most of the lesions are located at or near the stoma. These children are

otherwise well and require treatments when recurrent papillomata cause obstructive symptoms.

Adults requiring laser bronchoscopy are most commonly elderly males with a long history of tobacco abuse and a diagnosis of inoperable bronchogenic carcinoma. These patients often have all the stigmata of chronic obstructive airway disease and cancer, including weight loss, hypoxemia, hypercapnia, right heart failure, and cardiac arrhythmias. Also, they frequently have coexisting illnesses, such as diabetes and gastrointestinal disease, and often take several medications.

Patients in this adult population require careful preoperative evaluation, including a complete systems review and a thorough physical examination. Electrocardiography, arterial blood gas analysis, chest radiography, and biochemical and hematologic profiles are essential requirements when initially assessing these patients. Tomograms and computed axial tomography (CAT) scans of the chest are usually required to exclude those with lesions producing extrinsic compression of the airway lumen or destruction of the tracheal or bronchial wall. Laser treatment in cases of compression or destruction produce minimal benefit, and subsequent cicatrization can further complicate the clinical picture.³⁴

SURGICAL CONSIDERATIONS

Choice of Lasers

The main two choices of lasers are CO₂ and Nd:YAG. Both have a rapid thermal drop, but the extinction length is shorter for CO₂ than for the Nd:YAG. Therefore, the tissue adjacent to the laser beam is unaffected with the CO₂ laser, whereas 20 W of Nd:YAG laser can produce thermal damage 10 to 15 mm from the laser beam.¹⁰ This can cause tracheomalacia and other tissue damage below the laser beam site.^{16, 31} However, the Nd:YAG laser is poorly absorbed by hemoglobin, has deep tissue penetration, and will pass through a fiberoptic filament. For these reasons, it is the laser of choice for debulking procedures of lesions beyond the range of the rigid scope.⁶⁶ The CO₂ laser is rapidly absorbed by water and therefore has a very shallow tissue penetration, producing minimal edema in adjacent tissue.³³ Both lasers produce good hemostasis, but massive bleeding from a pulmonary artery perforation has occurred with the Nd:YAG^{46, 65} and the CO₂³⁴ laser. Recently, a nontoxic, flexible fiberoptic delivery system, consisting of a cladded combination of metallic halides, has been developed to deliver a CO₂ laser beam through a fiberoptic bronchoscope.⁴⁹ However, further experience is needed to prove the efficacy of this new laser delivery system.

Choice of Bronchoscope

The first laser surgery to the tracheobronchial tree utilized a rigid bronchoscope.⁵⁸ This is the instrument most often preferred by the

surgeon, because it (1) provides a better field of vision, (2) allows rapid cleansing of the lens, (3) yields a pathway for forcep removal of large pieces of tissue or blood clot, (4) offers steadier positioning of the neon-helium pilot beam, and (5) furnishes the most efficient route to treat hemorrhage with vasoconstrictor soaked cottonoids.^{13, 47} The rigid bronchoscope is completely nonflammable and circumvents the rare, but documented risk of intratracheal combustion of a fiberoptic bronchoscope.⁶ Many adaptations of the rigid bronchoscope have been produced to facilitate smoke evacuation via a suction port⁷ and to use jet ventilation for adequate oxygenation and ventilation during laser procedures.^{12, 43, 44, 52} Personne and coworkers⁴⁷ have modified a Negus rigid bronchoscope by welding two brass tubes to the luminal wall. One tube is for jet ventilation, whereas the other serves for suction and aspiration of fumes and smoke. The laser fiber is inserted in the biopsy channel of the bronchoscope.

It was the pioneer work of Hirschowitz and others,²² in Birmingham, that lead to the new clinical adaptations of fiberoptic endoscopy. In 1976, the first use of the flexible fiberoptic endoscope to deliver a Nd:YAG laser beam was described to treat upper gastrointestinal disorders.¹⁸ A few years later, Vourc'h and associates⁶¹ described the use of the Nd:YAG laser via the flexible fiberoptic endoscope to treat endobronchial lesions. The laser fiber can now be passed through a 27-mm channel of the flexible bronchoscope and follow a nonlinear course to the lesion. Our surgeons insert the fiberoptic bronchoscope through a rigid bronchoscope to maintain the advantages previously identified. Alternatively, it may be passed through a large bore cuffed endotracheal tube; yet fire is always a risk,⁶ particularly if polyvinylchloride endotracheal tubes are employed.⁴⁵

Surgical Results

In most series, the selection of cancer patients for laser treatment is based on criteria proposed by McDougal and associates³²: all other forms of treatment have failed and patients are not suitable for thoracotomy. Therefore, the results of "last-resort" endoscopic laser treatments are impossible to compare, because there are no alternative modes of therapy. In the series of 839 patients by Dumon and colleagues,¹³ they attribute their low mortality rate of 0.4 per cent and high palliation success rate to strict adherence to clearly defined safety principles, which include careful screening, use of the rigid bronchoscope, and preparations to treat hemorrhage. In another large series⁴⁶ of 604 patients with cancer, 16 perioperative deaths constituted a mortality rate of 2.7 per cent. The survival rate at 1 year was 25 per cent. McElvein and coworkers³⁵ reported on 135 patients with malignant disease treated over a period of 4.5 years. For the entire group the 1-year survival rate approximated 50 per cent. For those who expired in the first year, the average time of death was 4.3 months from the first laser treatment. One patient in their series survived 65 months.

The patients who benefit the most, albeit for a short period of

time, are those whose symptoms of airway obstruction are immediately relieved by laser vaporization of obstructing lesions. That is, laser bronchoscopy does not cure airway cancer but rather provides palliation.

Complications

The risk of endotracheal fire is always present.^{44, 52} However, with appropriate use of laser-resistant materials,⁴⁵ an ambient O₂ concentration of less than 50 per cent,^{38, 60} and the avoidance of combustible gases such as N₂O,^{21, 37} the potential risk is minimal.

Pulmonary hemorrhage^{35, 65} occurs most often when the lesion completely occludes the left or right mainstem bronchus. In these settings, the bronchial luminal direction is obscured and the bronchoscopist inadvertently lasers through the bronchial wall, perforating the pulmonary or bronchial vessels.²⁴ This hazard can be minimized by using the mapping technique described by Joyner and others.²⁴ Their method entails perforation of blind intrabronchial obstructions and then identification of the postobstructive bronchial remnant by injecting renografin. This "real time intrabronchial mapping technique" maximizes accurate direction of the laser beam. Another complication of laser beams penetrating the tracheobronchial wall is perforation of the proximal trachea, resulting in tracheoesophageal fistula and pneumothorax.¹⁹

Other complications include damage to normal tissue outside of the airway, postoperative tracheomalacia, smoke-induced pneumonitis,¹⁰ lower airway occlusion by tumor particles and necrotic tumor coagulum,²⁴ and postoperative airway obstruction secondary to perioperative edema.⁶⁵ This latter complication is more common with aggressive Nd:YAG laser surgery where the potential for thermal damage is greater than with the CO₂ laser.³¹ In one series,²⁴ all patients required at least one bronchoscopic procedure 3 to 5 days postoperatively to remove debris that could not be removed by normal mucociliary transport mechanisms or by coughing. Failure to remove this necrotic tissue will lead to ventilation-perfusion mismatch with resultant hypoxemia. Also, the tissue distal to the obstruction is vulnerable to infecting organisms leading to pneumonitis or lung abscess.

ANESTHETIC CONSIDERATIONS

The preoperative evaluation of patients for laser bronchoscopy is particularly important in order to avoid preventable mishaps. Old hospital charts, with records from previous general anesthetics, will give information regarding intubation and ventilation difficulties, tube sizes required, and any complication that could recur. Preoperative blood gas analyses will help to define the criteria that the anesthesiologist will use for extubation and then discharge from the recovery room.

In elderly cancer patients presenting for laser bronchoscopy, two

areas of particular concern in the preoperative evaluation are the status of the myoneural junction and left ventricular myocardial performance. Myasthenic syndrome (Eaton-Lambert syndrome) is an uncommon prejunctional disorder of the myoneural junction seen in some patients with carcinoma of the bronchus as well as in other organs.²⁷ These patients demonstrate enhanced sensitivity to depolarizing and nondepolarizing muscle relaxants.³⁹ Therefore, the dosages of these agents must be individualized for each patient by careful titration and the use of a peripheral nerve stimulator. The return of myoneural integrity must also be carefully evaluated. Early extubation and removal of ventilatory support prior to complete recovery of muscle strength will lead to retention of secretions, hypoventilation, and hypoxia in the immediate postoperative period. More commonly, however, these cancer patients are particularly sensitive to neuromuscular blocking drugs because of their cachectic and debilitated condition, resulting from their disease.

Careful evaluation of left ventricular performance is particularly important in patients with airway obstruction. The presence of obstructive processes in the tracheobronchial tree necessitates generation of increased negative intrathoracic pressures for adequate ventilation. Buda and associates⁵ have recently shown that an increase in negative intrathoracic pressure increases true left ventricular afterload. As the intrathoracic pressure becomes more negative, the left ventricular transmural pressure (the algebraic difference between the intraventricular and intrathoracic pressures) increases, causing increased work for the left ventricle during systole. Therefore, a patient with a compromised left ventricle and with superimposed airway obstruction is predisposed to failure and pulmonary edema. An electrocardiogram, a chest radiograph, and possibly a cardiology consult will be particularly useful.

The routine monitors used in patients for laser bronchoscopy include an EKG, automated noninvasive blood pressure device, peripheral nerve stimulator, end tidal CO₂ analyzer, temperature probe, and precordial stethoscope. One routine monitoring device that warrants particular mention is the pulse oximeter. We are currently using oximeters manufactured by Ohmeda and Nelcor and, like others,⁶⁷ we find this device to be invaluable. During the time of lasering, when the FIO₂ has been changed from 1.0 to less than 0.5 to reduce the risks of fire, the oximeter provides continuous information about adequacy of oxygenation. At oxyhemoglobin saturation levels of 90 per cent or less, we inform the surgeons to stop lasering while we switch to 100 per cent oxygen to re-establish adequate blood oxygen levels. Without this monitor, the anesthesiologist has no early signs of threatening hypoxia.

Some patients with chronic obstructive pulmonary disease and cancer should receive an arterial line for direct blood pressure measurements. Often, these patients have coexisting myocardial disease and are prone to sudden hypotensive episodes.⁵⁷ The common condition predisposing to hypotension is hypovolemia usually resulting

from poor nutrition and hydration. Intravenous (IV) fluid replacement prior to induction is particularly helpful to minimize the risks of hypotension. In addition, these patients often have slow circulation times. What may be a normal dose of an anesthetic drug in a healthy individual could produce an overdose in these patients, consequently leading to hypotension. Overzealous positive pressure ventilation, which produces hypocapnia and a decrease in venous return, is the other cause of a sudden drop in blood pressure.⁸ By continually assessing the arterial pressure, early detection leads to prompt therapeutic interventions, such as rapid IV fluid infusion or vasopressor administration. In all cases, we have a 0.004 per cent solution (10 mg in 250 ml) of phenylephrine available.

Equipment

In addition to all the routine equipment required to administer a general anesthetic, the following items are essential: (1) large H tanks of compressed air and 100 per cent oxygen, both of which are connected to a system of hoses that allow easy and alternative delivery from one tank or the other; (2) a modification of the Sanders'⁵⁰ jet ventilation device to deliver the oxygen or the compressed air through a bronchoscope, laryngoscope, or a catheter placed through the cricothyroid membrane⁴; (3) special eye protection appropriate for the specific laser in use for all operating room personnel; and (4) an assortment of fire-resistant endotracheal tubes.^{37, 42}

Induction of Anesthesia

After an appropriate equipment check and preparation for anesthesia, induction can be achieved with sodium thiopental,^{12, 65} etomidate,^{7, 17} propanidid,¹⁵ ketamine,^{3, 24} alfadione,¹³ and narcotics,²⁹ either as the sole agent or in combination. The author finds the sequence of 0.07 mg per kg midazolam,^{2, 64} 0.2 to 0.5 µg per kg of sufentanil, and 1 to 2 mg per kg of sodium thiopental particularly effective to provide a smooth induction, protection from cardiovascular effects of laryngoscopy, intubation or placement of bronchoscope, and prevention of intraoperative recall. Lidocaine, 1.5 mg per kg, is administered by IV or more commonly, intratracheally, during laryngoscopy. IV pentothal or narcotic is administered repeatedly in accordance with the hemodynamic response. The amnestic effect of midazolam lasts 45 to 60 minutes and the dose should be repeated at that time to avoid the risk of recall.² Potent inhalation anesthetics can be employed if standard means of convection ventilation are used.¹² However, in all instances, nitrous oxide must be avoided, as it will support combustion⁶⁴ and has been associated with ignition of the endotracheal tube in one case report.²¹ In children with pre-existing tracheostomies, we prefer to induce anesthesia with halothane via the tracheostomy tube and then switch to enflurane or isoflurane after induction to minimize the risk of halothane-induced myocardial sensitivity to catecholamines.²⁵

Occasionally, the surgeon may prefer to use the Nd:YAG laser

and the flexible fiberoptic bronchoscope without general anesthesia²⁴ because endobronchial Nd:YAG laser treatment is painless.⁵⁹ To maximize patient comfort, we apply 10 per cent cocaine to the nasal cavity, administer glossopharyngeal⁹ and superior laryngeal²⁰ nerve blocks with 2 per cent lidocaine, and inject 6 ml of 2 per cent lidocaine intratracheally through a cricothyrotomy. In conjunction with IV sedation with midazolam and occasionally sufentanil, these regional anesthetic procedures provide patient comfort. Midazolam minimizes recall. One word of caution, however: the combination of midazolam and sufentanil in patients during monitored anesthesia care will often depress ventilation with resultant hypoxia; this re-emphasizes the need for the pulse oximeter as a routine monitoring device.

Mode of Ventilation

Patients requiring general anesthesia for laser bronchoscopy can be ventilated using the standard semiclosed circle absorber system to deliver fresh gases through an endotracheal tube or via the side arm of a standard bronchoscope equipped with a cuff to seal the airway.⁶² With this mode, adequate anesthesia and analgesia can be maintained with any inhalational anesthetic agent. Muscle relaxants may or may not be required with this approach. In 1967, Sanders⁵⁰ presented a landmark paper describing ventilator adapters for bronchoscopes and, thus, introduced jet ventilation into clinical practice. These adapters were connected to compressed air or oxygen tanks to deliver gas under pressure through the proximal end of the bronchoscope. Compressed air or oxygen under 55 lb per square inch (psi) will flow as a jet stream at a rate of 500 ml per second through a 16-gauge catheter.⁵⁵ When this jet is introduced into a tube in its axial direction, subatmospheric pressure is generated at the proximal orifice, thereby entraining room air. When the jet is applied to the bronchoscope, the net pressure generated in the distal airway will vary according to the force of the jet and the diameter of the bronchoscope. According to Sanders,⁵⁰ a jet pressure of 50 psi delivered through a 3.5-mm bronchoscope generates 45 cm H₂O pressure, whereas the same jet through an 8-mm bronchoscope generates only 27 cm H₂O pressure. Therefore, the risk of barotrauma increases with bronchoscopes of smaller diameter. Several authors have described their own variation and modification to Sander's original presentation. Special ventilators have been manufactured to adapt to narrow conduits welded to the luminal wall of a bronchoscope^{44, 46, 62}; and jet adaptors have been manufactured to connect to the 15-mm side arm ventilation port. Most clinicians manually apply 10 to 20 jets per minute with a duration of 0.5 to 1.0 second per jet³⁴ while assessing adequacy of ventilation. High frequency jet ventilation (300 bpm) has been used successfully for laser bronchoscopy.⁶¹ However, Vourc'h and coworkers⁶² employed it for patients with bronchial stenosis and noted an association between the high-frequency mode and modest hypercapnia. Therefore, manual jet ventilation was the preferred mode in their bronchial stenosis patients. At the University of Alabama at Birmingham, we place the Sanders

attachment to the side arm of the bronchoscope and manually jet ventilate 10 to 20 times per minute. This system works equally well for adults and children.

We have observed that one frequent cause of hypoxemia and desaturation during jet ventilation is chest wall rigidity. This may be due to the narcotics employed⁵⁴ or light anesthesia during recovery of neuromuscular function. Therefore, we always employ nondepolarizing muscle relaxants, such as vecuronium or atracurium. Succinylcholine infusion may also be employed; however, phase II block looms as a possible consequence when the total dose exceeds 10 mg per kg in children¹¹ and as low as 200 mg in a 70-kg adult.²⁶ In such cases, prolonged ventilation or anticholinesterase administration will be required.

At the conclusion of laser surgery, the bronchoscope should be left in the trachea to identify and manage delayed bleeding or accumulation of secretions. As the patient recovers from neuromuscular blockade and anesthesia, the bronchoscope is removed and ventilation is supported with mask and bag. In case of a delayed recovery, the trachea is reintubated with a large bore endotracheal tube and ventilation maintained with a mechanical ventilator until recovery is complete. Judicious use of naloxone may be indicated.

Complications

Many of the potential complications have been mentioned in earlier discussions and will be summarized. Fortunately, as our experience increases, the complications are less frequent.

Bleeding. Bleeding may be fatal if the pulmonary vessels are penetrated during laser treatments.⁴⁵ Postoperative bleeding from the lesion site is rare because of the coagulation properties of the laser.

Hypoxia. This is most often caused by inadequate ventilation owing to malalignment of the jet stream or to chest wall rigidity. Occasionally, the anesthesiologist must instruct the surgeon to stop lasering and withdraw the bronchoscope so that its distal end is above the carina. A few minutes of jet ventilation with 100 per cent oxygen will restore adequate oxygen saturations in most cases.

Hypotension. Relative hypovolemia, abrupt lowering of CO₂, cardiac failure, or arrhythmias, and relative overdose of anesthetics are common causes.

Fire. This hazard can be minimized by lowering FIO₂ to less than 0.5 (at UAB, we jet ventilate with compressed air during laser treatments) and by avoiding combustible materials, such as polyvinylchloride.⁶

Barotrauma. Pneumothorax and pneumomediastinum may result from laser penetration of the airway or excessive inflation pressures, or both.⁴⁶

Awareness. This is a particular problem during IV anesthesia. Midazolam is particularly valuable to prevent recall.^{2, 48}

Failure to Recover Neuromuscular Integrity. Relative overdosage of muscle relaxant, phase II block, residual general anesthetic

effects, patient debilitation, or the myasthenic syndrome are factors to consider. Significant serum levels of aminoglycoside antibiotics or lidocaine⁶⁶ may prolong residual neuromuscular block.

Airway Edema. Airway edema can occlude segmental bronchial or mainstem bronchial lumina early in the postoperative period causing respiratory failure and death due to hypoxemia-related cardiovascular complications.¹³ Paes and others⁴⁴ recommend prophylactic use of dexamethasone or methylprednisolone.^{15, 34, 44}

Secretions. Airway instrumentation and laser surgery stimulates copious secretions that not only impair effective laser resection (particularly with the CO₂ laser), but also lead to respiratory failure due to airway obstruction. Prophylactic anticholinergics are helpful if the myocardium can tolerate the tachycardia commonly resulting from these agents.

Arrhythmias. Most arrhythmias encountered during laser bronchoscopy result from endogenous catecholamine release during airway instrumentation in inadequately anesthetized patients. Appropriate IV doses of narcotic analgesics and topical application of local anesthetics minimize this complication.

Bronchospasm. Many of the adult patients have chronic obstructive pulmonary disease associated with their airway cancers. Airway instrumentation will increase bronchomotor tone and airway resistance through activation of upper respiratory and axonal reflexes.¹ Topical local anesthesia and anticholinergic agents will block the afferent and efferent limb of these reflexes and, when used with an adequate depth of anesthesia and with β_2 agonists, will limit bronchospasm. Many of our cases are completed on an outpatient basis. However, significant complications such as these, if persistent, require admission to the hospital.

SUMMARY

The CO₂ and Nd:YAG lasers are most commonly used to treat endobronchial lesions. The patients selected for laser treatment are symptomatic because of inoperable obstructive lesions. The surgeon can treat these lesions using either a rigid or flexible fiberoptic bronchoscope. Local anesthesia is sufficient for fiberoptic laser bronchoscopy, whereas general anesthesia is required when the rigid bronchoscope is employed. The main complications encountered are hemorrhage, hypoxia, hypotension, fire, barotrauma, awareness, residual neuromuscular block, airway edema, secretion accumulation, arrhythmias, and bronchospasm. Careful preoperative evaluation, intraoperative monitoring, and individualization of choice and dose of agents selected will minimize adverse complications. Albeit, the procedure is primarily palliative, the relief of symptoms seen in the majority of patients who receive bronchoscopic laser treatments should encourage clinicians to approach patients with optimism as they offer hope.

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Anesthetic Management of Patients Undergoing Endoscopic Laser Surgery

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LASER is an acronym, derived from Light Amplification by Stimulated Emission of Radiation. It was discovered in 1958 by American physicists Townes and Schawlow, who subsequently received the Nobel Prize. The most commonly used clinical laser, a CO₂ laser, was developed in 1964 by Patel. Jako, in 1968, pioneered the first endoscopic use of the CO₂ laser in an experimental study on the canine larynx. He further introduced laser surgery on the human larynx in 1972.¹

Laser surgery is thought to be very precise, destroying diseased tissue while leaving normal tissue essentially unaffected 50 μ m away (the width of seven red blood cells lying side by side). As a result, less pain, edema, and scarring may result in comparison to traditional surgical techniques. It also allows more rapid healing. The tissue penetration or burn produced by a laser depends on the power employed and duration of burn. A typical laser setting approximates a power output of 5 to 25 W with a duration of burn of 1/20 of a second (50 msec). CO₂ lasers are particularly advantageous for endoscopic procedures because the beam may be directed down open-tube endoscopes. This method produces an invisible beam that affords the surgeon an unobstructed view of the operated area, facilitating access. The laser beam is transmitted by means of an articulated arm through a microscope controlled by a micromanipulator. Thus, a CO₂ laser is most easily applied for pathology of the upper airway and proximal trachea. The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, which produces a greater depth of burn, is used mainly for tumor debulking. Because the Nd:YAG beam can be transmitted via a fiberoptic cable through a flexible endoscope, it is useful for resection of lower tracheal and bronchial lesions.

Laser surgery provides a less bloody field because the beam cau-

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terizes superficial vessels. CO₂ lasers coagulate vessels less than 1 mm in diameter whereas Nd:YAG lasers coagulate vessels of larger diameter, thus lowering the risk of intraoperative and postoperative bleeding. In summary, the advantages of laser techniques for endoscopic surgery include (1) microscopic precision, (2) hemostasis, (3) endoscopic access, and (4) reduced edema and scarring.

TECHNOLOGICAL CONSIDERATIONS

Physics of Lasers

Laser light is intense, monochromatic, and highly collimated. The atoms of a single element usually emit radiation at only one specific wavelength and frequency. The electrons of an atom occupy certain discrete quantized locations known as orbits or shells. The lowest energy of an atom is associated with the normal orbit of its electrons, the so-called "ground state." Energy states at higher levels are termed "excited states." These orbits have different energies, with the orbits farthest from the nucleus having the greatest energy. An electron

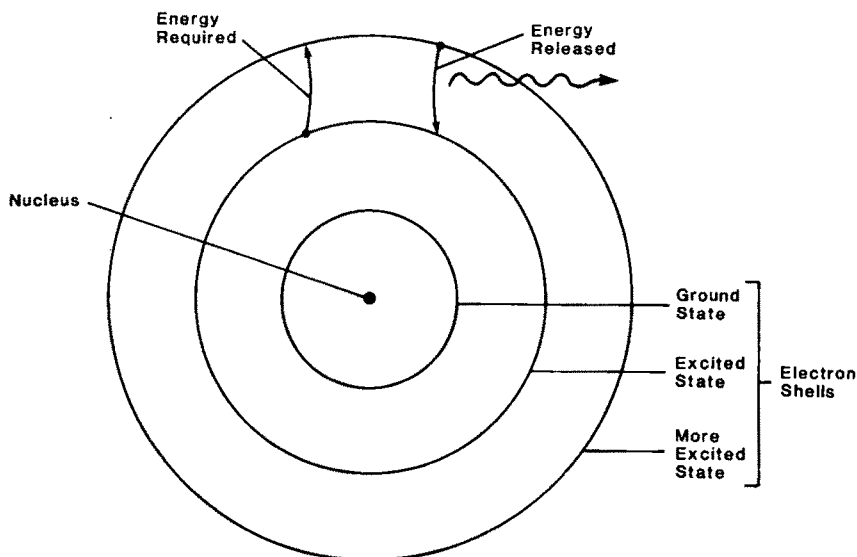


Figure 1. Electron shells of different energies are depicted surrounding the nucleus of an atom. The electron shell closest to the nucleus is labeled "ground state" and contains the least amount of energy. As electrons move to shells farther and farther away from the nucleus, greater and greater energy is carried in them. Thus, the electrons that are circulating in the shell beyond ground state are labeled as "excited," and those that are in shells even farther away from the nucleus are identified as being even "more excited." Energy absorbed by the atom will move an electron from one energy shell to a higher energy shell and similarly, as an electron moves from a higher energy shell to a lower one, energy is released as a result.

undergoes a transition from one state to another as a result of absorbing energy or releasing radiation (Fig. 1). Any molecule in an excited state tends to lose energy, much as water tends to lose energy by running downhill. One of the principal ways by which an excited molecule loses energy is by emission of a light wave or photon. As an electron moves from a higher energy level orbit to a lower one, it loses energy by emission of a photon. The wavelength of a given photon results from the energy difference between the excited state of its electron from which it originates and the lower energy state (not necessarily the ground state) to which it moves (Fig. 2). The wavelength frequency of this radiation is different for and characteristic of each atom. Therefore, an atom emits or absorbs a single photon (or quantum of radiant energy) when it changes from one energy state to another, and the energy of the photon is proportional to the energy difference between the two states. If the emission emanates from the part of the electromagnetic spectrum to which the eye is sensitive, we see it as light. If not, the laser beam is invisible.

A laser device generally consists of a tube with mirrors at either end; one mirror ideally is totally reflective and the other is partially reflective (Fig. 3). The amplifying medium, the substance from which the laser derives its name, lies between. In a gas laser, such as the CO₂ laser, the tube is filled with a gaseous medium that becomes

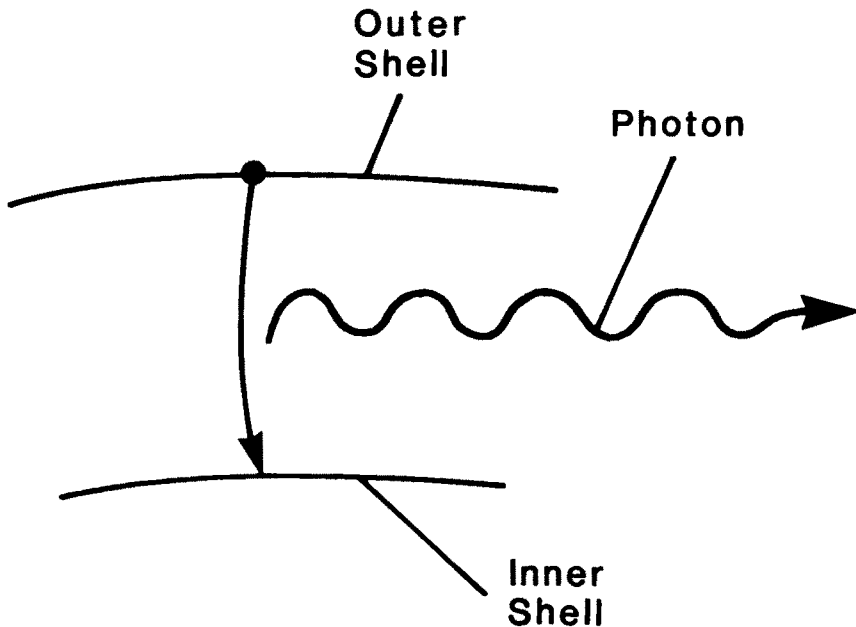


Figure 2. Depicted in closer detail are an outer shell and an inner shell for electron movement around the nucleus of an atom. As an electron moves from an outer shell to an inner shell it loses energy by releasing a photon. The wavelength of a given photon is specific to the energy difference between the outer shell and inner shell of the atom and is different for and characteristic of each atom.

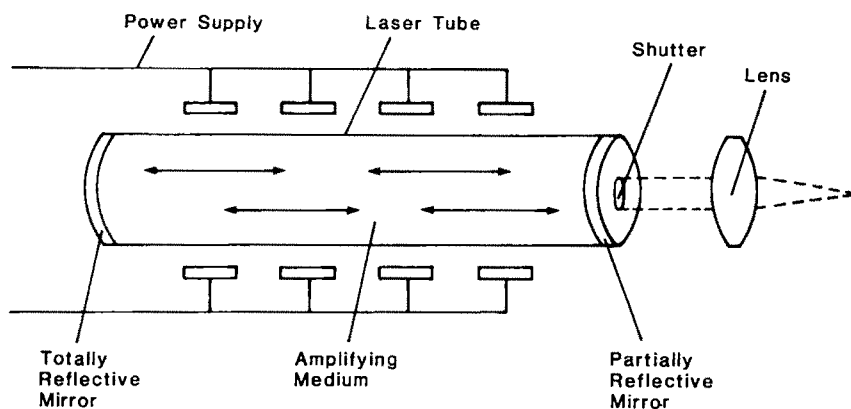


Figure 3. A schematic diagram of a laser tube typical of a CO₂ laser. The laser tube is generally a long slender tube with ideally a totally reflective mirror on one end and a partially reflective mirror on the other end. The amplifying medium, the substance from which the laser derives its name, is energized with some sort of power supply. The material inside releases energy in the form of photons, which eventually align along the longitudinal plane of the laser. A portion of the laser energy is delivered through the partially reflective mirror controlled by a shutter mechanism and focused through a lens device on the target tissue.

excited by high-voltage AC or DC electrical current. The material of the laser media may also be a solid or liquid. By energizing the medium, photons of a single wavelength (monochromatic) are emitted and by end-to-end reflection eventually assume the same direction. As the photons contact other energized atoms, they stimulate further release of identical photons (stimulated emission) aligned in the same direction with the same frequency (coherence). The laser output released through the partially reflective mirror (which transmits a percentage of the contained laser light) is controlled by some type of shutter mechanism. The laser beam may then be directed through a series of lenses for focusing on an identified target.

Common Medical Lasers

There are many medically useful lasers in clinical use. The effect that a particular laser has on human tissue depends on its wavelength and power density. As discussed previously, the medium of the laser, from which the laser derives its name, determines the wavelength of the energy emitted. In general, laser beams with greater wavelengths yield greater absorption of energy by tissue and greater conversion of that energy to heat. Power is the energy delivered per unit of cross-sectional area and is usually indicated as watts per cm². As shown in Table 1, the CO₂ laser has an output at a wavelength of 10.6 μm and is generally used in a power range of 3 to 50 W. The argon laser has an output at two separate wavelengths of approximately 0.5 μm whereas the Nd:YAG laser has an output wavelength of 1.06 μm .

Table 1. *Types of Lasers*

LASER TYPE	BEAM		FIBEROPTIC TRANSMISSION	LASER MODE	ABSORBED BY
	Wavelength (μm)	Color			
Gas					
CO ₂	10.6	Invisible (far infrared)	No	Pulsed/continuous	Water of all tissues
Argon	0.488/0.515	Blue-green	Yes	Continuous	Melanin/hemoglobin
Helium	0.633	Red	Yes	Continuous	Used for alignment of other lasers
Solid					
Crystalline					
Ruby	0.695	Red	Yes	Pulsed	Melanin/cytochrome
Glass					
Nd:YAG (neodymium yttrium-aluminum- garnet)	1.06	Invisible (near infrared)	Yes	Pulsed	Pigmented tissue

CO₂ laser beams may be focused and reflected but cannot be transmitted through glass or quartz and thus may not be employed via fiberoptic transmission. Characteristically, the energy of lasers with wavelengths of 2.5 μm or larger (such as the CO₂ laser) will be absorbed by water or the water content of blood and tissues. Because human tissue is 80 per cent water, laser energy is absorbed by tissue water, rapidly raising its temperature, denaturing protein, and eventually vaporizing tissue. This mechanism accounts for a misdirected laser beam that contacts the cornea of patients or operating room personnel, producing corneal injury. On the other hand, the energy of ruby, argon, or other lasers with wavelengths less than 2.5 μm is not absorbed by water. These laser beams may therefore readily pass through the cornea and be employed by ophthalmologists to produce selective vaporization of the pigmented retina. The Nd:YAG laser emits invisible, near-infrared light with a wavelength 1/10 that of the CO₂ laser. This light is better absorbed by pigmented tissue and has reduced absorption in nonpigmented tissue. A major advantage of the Nd:YAG laser over the CO₂ laser is that the Nd:YAG laser can be conducted through fiberoptic instruments. Hence, the Nd:YAG laser can be used through a fiberoptic bronchoscope for removal of tissue in the tracheobronchial tree.

SURGICAL AND ANESTHETIC CONSIDERATIONS

Surgical Applications

Lasers have been employed in gynecologic, neurosurgical, ophthalmologic, urologic, and plastic surgery. Surgical application of lasers by otolaryngologists is rapidly expanding. In this field, endoscopic laser surgery is best employed to remove laryngeal papillomas, laryngeal neoplasia, laryngeal webs, and also to resect subglottic stenoses and subglottic hemangiomas. Less frequent applications include tumor debulking, resection of vascular lesions, and epiglottectomy. Laser excision of tonsils is discrete and may lead to fewer postoperative complications, but is time consuming and not viewed as practical by many otolaryngologists.

Hazards of Laser Use

Although lasers contribute significant advantages to the management of certain surgical procedures, they also pose a risk to patients and health care personnel. These risks include injury to eyes and skin, electrical shock, fire, explosion, and injury from noxious fumes.

Injury to Eyes and Skin. A misdirected laser beam contacting the eye of the patient or health care personnel may result in impaired vision or blindness. The nature of the injury is determined by the wavelength of the laser employed as well as the power absorbed. For example, energy absorbed from a CO₂ laser primarily produces corneal injury, whereas energy from a Nd:YAG laser will likely produce

injury to the retina. Cutaneous injury from absorption of a misdirected laser beam can produce damage ranging from mild erythema to full-thickness burns.

Electric Shock, Fire, and Explosion. As will be discussed in more detail later, laser beam contact with flammable materials such as endotracheal tubes, anesthetic tubing, surgical drapes, and sponges can result in ignition and fire. In addition, the laser equipment itself (laser tubes and flash lamps) may explode. Contact with the high-voltage power source of laser equipment may result in electrical injury or electrocution.

Noxious Fumes. Smoke and products of combustion (plume) are generated by vaporization of tissue and may be harmful if not scavenged.^{5, 28} These fumes are potentially mutagenic and may transmit infectious disease.²⁹ Currently, there is concern that live DNA particles may remain in vaporized tissues and may thus be able to transmit the AIDS virus or other virally mediated diseases. The smoke and products of combustion also impair the vision of the surgeon and present a secondary hazard of ignition if sparks and hot debris are shot about by the explosive vaporization. Constant suctioning should be used to remove as much smoke as possible for the environment to reduce its inhalation by the patient and operating room personnel. However, these smoke particles may heat or clog suction lines and necessitate costly repairs. Thus, special filters in suction lines are advisable.

Complications Specific for Endoscopic Laser Surgery

Endoscopic surgical procedures have a number of associated complications. These include airway obstruction, hypoventilation, aspiration of resected material, hypertension and dysrhythmia associated with the very stressful procedure of protracted laryngoscopy, and dental trauma. In addition, as we will discuss later, each anesthetic technique recommended for endoscopic laser surgery is associated with its own set of complications.

Endoscopic laser devices may not only damage normal tissue, owing to misdirection of the beam or reflection of the beam from a reflective surface, but may also damage equipment not capable of withstanding its impact. Gupta et al¹¹ demonstrated that a relatively weak laser beam of only 2 W power and 200 msec duration, if reflected from an endotracheal tube that had been wrapped with reflective metallic tape, would produce superficial burns of the trachea in a canine model. Laser radiation increases the temperature of absorbent material and thus, flammable objects must be kept out of the way and protected from the laser beam. For example, in a survey of 47 otolaryngologists, Fried⁶ reported a variety of complications associated with the use of lasers for endoscopic surgery. These included endotracheal tube explosion, laryngeal scarring, facial burns, pneumothorax, subcutaneous emphysema, endotracheal tube cuff ignition, cottonoid ignition, and hemorrhage.

Protective Measures

Damage to the eyes is an easily prevented complication. Patients and personnel in the vicinity of a laser beam anywhere in the operating theatre must wear eye protection. For a CO₂ laser, most forms of plastic or eye glasses are adequate because the CO₂ wavelength will be absorbed by them. However, other types of lasers will penetrate these plastic or glass materials and still produce ocular injury. It is therefore important to employ eye protection designed specifically to absorb the wavelength of the laser beam in use. For example, protective glasses in the blue-green spectrum are necessary when using the Nd:YAG laser. Special filters can also be employed for flexible endoscopes. It is also important to remember that, with almost all protective goggles or glasses, that the protection is limited and that these eye glasses can absorb enough energy to melt and should not be considered 100 per cent protective. Glasses selected must be comfortable (so that they will be worn) and must also protect the peripheral vision of the eye from transmission of misdirected laser beams. Access to the areas where lasers are in use should be limited. Windows in doors or scrub areas should be covered. Doors should be locked to prevent accidental entry into the room during laser procedures. Warning signs should be posted at the door of the room in which a laser is being used and devices can be installed to automatically turn off the laser when the doors open.

Because only minor skin injury results from cutaneous absorption of laser radiation, there are no specific recommendations regarding protective clothing for operating personnel. For patients, however, a direct, high-intensity laser contact may produce injury, and therefore skin and mucous membranes must be protected with saline-soaked sponges or gauze. Surgical instruments and other materials used in the path of the laser beam ideally would have low specular reflectance to reduce the likelihood of damage produced by reflected laser beams.

The laser device itself requires regular equipment maintenance to ensure its optical alignment and to prevent equipment malfunction. Health-care facilities that use lasers should have a formal safety program directed by a laser safety committee. The committee must include a laser safety officer who has the knowledge, authority, and responsibility to monitor the use of lasers and to enforce measures in controlling laser hazards. Other members of the committee may include hospital administrators, physicians, and technicians. Such a committee should establish standard operating procedures for each laser system and oversee the credentialing of personnel operating lasers.

Management of Ventilation During Endoscopic Laser Surgery

During endoscopic ENT laser surgery, a relatively motionless surgical field must be provided by the anesthetists and surgeons who share it. Historically, a variety of techniques have been employed in an attempt to assure adequate ventilation during endoscopic proce-

dures of the larynx. These have included a cumbersome device to produce negative intrathoracic pressure by a reverse ventilation technique similar to that employed in an artificial lung while the airway remains unprotected. Also, spontaneous respiration under deep anesthesia has been attempted. With this technique, mask anesthesia is used to obtain a deep level of anesthesia with an inhalational anesthetic agent followed by mask removal and surgical exposure of the airway. This presents problems of a moving target for the surgeons (due to spontaneous ventilation) and poor airway control by the anesthesia team. Anesthesia persists for only a short duration of time before the patient awakens requiring reinduction of anesthesia. A modification of this technique employs nasotracheal insufflation of oxygen and an inhalational anesthetic agent. This brings forth the same problems of poor airway control and, in addition, anesthetic pollution of the operating room and surgical field. Other techniques for management of ventilation during endoscopic laser surgery include modifications of endotracheal tubes to protect the external surface of a conventional endotracheal tube, utilization of a noncombustible tube, or delivering anesthesia without an endotracheal tube, using jet venturi ventilation.

Special Endotracheal Tubes

Endotracheal tubes of small caliber but of normal length have been developed for adult-type laryngeal surgery (MLT tubes). However, traditional polyvinyl chloride (PVC) endotracheal tubes are flammable and subject to ignition when struck by a laser beam, just as is human tissue. Catastrophic intraluminal ignition of endotracheal tubes causing blowtorch-type fires have been reported.⁷

PVC is a thermoplastic material that melts at a lower temperature than either red rubber or silicone tubes due to earlier penetration of the material by the laser beam. The environment provided by anesthesia gases, which contain a high FIO_2 , makes fire more likely. Also, HCl gas is a known product of PVC combustion.²⁸ As a result, if a PVC endotracheal tube is ignited by a laser device, not only does the trachea suffer heat, fire, and smoke damage, but also chemical damage from HCl gas.

The use of a red rubber Rusch tube, instead of a PVC tube, has gained popularity for laser surgery because rubber tubes may be less flammable and require greater laser energy to ignite. More importantly, the products of combustion of a red rubber tube are less toxic. Gupta et al¹¹ have shown that a PVC tube when ignited in a high ambient O_2 environment will burn like a blowtorch, whereas red rubber tubes tend only to smolder, char, and melt. Present controversy regarding the preferred endotracheal tube (red rubber or plastic) is moot. The important fact is that both kinds of tubes can be ignited when used in the high FIO_2 environment of anesthetic gases. Intraoperative fires have occurred with both types of tubes and therefore if either one of these types of tubes is selected, special protection must be employed in order to reduce the risk of ignition.

Norton introduced a vertebrated metal endotracheal tube that has the advantage of being nonflammable.¹⁹ However, metal endotracheal tubes have the potential for specular reflection of a misdirected laser beam. They also have the disadvantages of being technically cumbersome and difficult to insert and possibly traumatic to the vocal cords and tracheal mucosa. In addition, they are noncuffed, and their imperfect hinges may allow leakage of airway gas that causes operating room pollution and possibly increases the risk of laser-induced fire. In general, they have a smaller inner-to-outer diameter ratio.

A recent development is the so-called "Laser Shield" endotracheal tube, a laser-resistant endotracheal tube manufactured by Xomed, Inc. This tube contains metallic particles in a silicone base, allowing it to reflect a portion of a misdirected laser beam, thus increasing its resistance to ignition. Another advantage is that the reflection of laser light tends to be relatively diffuse rather than specular. This tube resists ignition with single pulses of 1-second duration and up to 25 W in power, regardless of ambient oxygen tension.⁷ Ignition is nevertheless still possible with absorption of laser beams of greater energy.

Two other entries into the laser endotracheal tube market include those manufactured by Bivona and Mallinckrodt. These tubes are similar to the Norton device in that they are also flexible and metallic. One tube is coated with a silicone sheath, whereas the other is uncovered. Both have a matte finish that tends to reduce specular reflection of laser beams, making injury in tissue receiving a reflected laser beam less likely. As will be discussed, both tubes have been designed with a special cuff to maintain airway protection and ventilation.

Modifications of Traditional Endotracheal Tubes

If a plastic or rubber tube is selected for airway protection during CO₂ laser surgery, it should be modified to make it even more resistant to laser ignition. Several modifications have been suggested. These include wrapping the endotracheal tube in muslin or metal foil.²⁵ The muslin is soaked in water or saline prior to endotracheal intubation. The water will dissipate laser energy, making ignition from contact with a misdirected laser beam less likely. The tube wrapping must be kept moistened throughout the procedure by intermittently injecting water onto the muslin with a syringe or by using a small catheter, such as an epidural catheter placed under the muslin.¹⁶ Disadvantages of muslin-wrapped tubes include their bulkiness, need for repeated moistening, and increased risk of ignition should drying occur.

A commonly employed technique uses a red rubber Rusch endotracheal tube wrapped with either aluminum or copper reflective tape. The tube is wrapped in a spiral fashion beginning near the tip or cuff and ending high on the tube where risk of laser misdirection is minimal. Tape edges are smoothed to decrease soft-tissue trauma, and the foil is trimmed. Aluminum tape may be found labeled as

"Sensing Tape" manufactured by Realistic Corporation or 3M. Gupta et al¹¹ tested many different varieties of 3M aluminum reflective tapes and found nos. 392 and 393 ineffective in preventing laser ignition of red rubber tubes. 3M no. 64 tape is 1-inch wide and wrinkles during wrapping and therefore is not suitable. 3M no. 51 tape is brittle and adheres poorly to endotracheal tubes. 3M no. 65 was found to be the best for endotracheal tube wrapping. Although aluminum tape is satisfactory, copper tape has the highest coefficient of reflectivity for infrared wavelengths and has been shown to be more malleable and superior to aluminum in endotracheal tube protection.²⁷ Copper tape is available at art stores, craft shops, and radio supply stores, whereas aluminum may be found at radio supply stores. Tape widths of 0.5 to 1.0 cm make for easiest wrapping.

Employing endotracheal tube wrapping has the disadvantage of possible wrap aspiration. Wrapping also decreases the pliability of the endotracheal tube making it more prone to kinking and obstruction. Rough edges that may be created can abrade the mucosa. If the tube is cuffed, the cuff itself cannot be wrapped. Errors in wrapping may leave areas of the endotracheal tube unprotected from the laser beam. Thus, the potential for tube ignition still exists, if the period of burn is long or if a small area of the endotracheal tube lacks protection. In addition, shiny reflective tape may effectively reflect the laser beam from the tube but burn other areas of the larynx or other portions of the airway.¹¹ As a result, a tape with a matte finish would be ideal. The user must also be warned that many tapes now have the same appearance as the metallic coated tapes but do not possess metallic reflective capability. Instead, they will absorb the energy of a laser beam just like any other plastic material.²⁷ I suggest that if you purchase any of these "reflective" tapes, to ensure that they are, in fact, metallic and reflective, by testing a small portion of the tape in the operating room with a laser beam (for flammability and reflectivity) prior to patient use. A muslin-wrapped endotracheal tube has the advantage of reduced likelihood for reflection injury, but requires attention to ensure that it constantly remains moist.

All endotracheal tubes (except metal) are vulnerable to thermal damage when exposed to the Nd:YAG laser.³¹ Wrapping endotracheal tubes with silver reflective tape does not protect them from the Nd:YAG laser. Clear PVC tubes are resistant to damage from the Nd:YAG laser because the laser passes through relatively unabsorbed. This is in contrast to their flammability when exposed to the CO₂ laser. However, clear tubes are not immune to damage because soiling of the tube with blood or tissue or markings manufactured on the tube create coloration that enhances absorption of energy.⁹ Endotracheal tubes should be avoided when using the Nd:YAG laser in the tracheobronchial tree, unless the laser beam can be delivered distal to the end of the endotracheal tube.¹⁰

Importance of Inspired Gas

A useful method of fire prevention restricts the fractional concentration of inspired oxygen. Because O₂ supports combustion, it is

a common misconception that reducing the FIO_2 with N_2O will make laser ignition of endotracheal tubes less likely. Several studies^{7, 13} have shown that N_2O supports combustion just as readily as O_2 . Any gas mixture containing O_2 and N_2O should be treated as equivalent to pure O_2 regarding the likelihood of ignition during laser surgery. Oxygen must be diluted with room air, nitrogen, or helium to effectively reduce flammability.¹⁷ During laser surgery, an FIO_2 of 30 per cent or less has been recommended to reduce combustibility of endotracheal tubes, if that concentration is consistent with adequate patient oxygenation.³² However, many tubes will burn in as little as 25 per cent oxygen.² Recently, Pashayan and Gravenstein²⁴ selected helium as the best of all gases for oxygen dilution in retarding endotracheal tube fires. Because of its high thermal diffusivity, helium decreases the heat of materials in contact with the laser beam and retards endotracheal tube ignition longer than nitrogen. They also draw the user's attention to the fact that the radio-opaque barium sulfate stripe, which runs the length of commonly used PVC endotracheal tubes, appears to be more vulnerable to laser ignition than the rest of the endotracheal tube. To make ignition less likely, all oil-based ointments used to lubricate endotracheal tube must be avoided because they are combustible and can be ignited by a laser beam.

Management of Endotracheal Tube Cuffs

Endotracheal tube cuffs should be inflated with saline or water rather than air because saline or H_2O more rapidly dissipates heat from the area of the cuff in contact with the laser beam. Saline acts as a heat sink and tends to prevent combustion.¹⁸ Also, saline would lend to fire suppression, should combustion occur. The liquid that is used to fill the cuff may be colored with a small amount of methylene blue. This alerts the surgeon to the presence of a disrupted cuff by the laser beam. Otherwise, release of the liquid from the endotracheal tube cuff may go unnoticed, and members of the anesthesia team would needlessly search for other sources of gas leakage.

If the laser beam contacts the endotracheal tube cuff, the cuff would deflate and loss of airway protection would result. The two newest endotracheal tubes for laser endoscopy have design features to reduce this possibility. The "Fome" cuffed laser endotracheal tube manufactured by Bivona contains spongy foam that should also be inflated with H_2O or saline when used for laser surgery. This tube has the theoretical advantage of remaining in its natural inflated position, even if a leak in the cuff has been produced by a misdirected laser beam. The burn characteristics of this cuff are untested. Similarly, the new laser tube from Mallinckrodt is designed with two separate endotracheal tube cuffs (one proximal and one distal), each of which should be filled with saline or another liquid. The tube is designed so that should laser-beam contact deflate the proximal cuff, the second cuff would remain inflated and maintain airway protection.

In general, when employing a cuffed endotracheal tube for airway maintenance during endoscopic laser surgery, some sort of cottonoid

or pledget should be applied by the surgeon proximal to the endotracheal tube cuff to absorb a misdirected laser beam. Of course these cottonoids or pledgets must be kept moist at all times. Case reports have described cottonoids inadvertently left in the airway causing respiratory obstruction.³⁰ A suture or wire attached to the cottonoids or pledgets will assist in their removal but will also require constant moistening if containing a flammable material.

Fire Management

If an endotracheal tube ignites during the operation, the tube should be disconnected from the breathing system and immediately removed from the patient. Injury to the tracheobronchial tree occurs as a result of heat, smoke, and the toxicity of the products of combustion.²¹ Some authors suggest that to minimize spread of fire and to keep toxic products of combustion from being inhaled, the oxygen supply to the airway should be disconnected prior to removal of the endotracheal tube.²³ Others suggest that saline or water should be injected down the tube prior to tube removal. My personal approach would be to remove the burning tube as rapidly as possible followed by an immediate flooding of the field with saline to ensure no further fire damage. Ventilation may then be resumed by mask and the trachea reintubated. The patient should then undergo bronchoscopy to assess the extent of injury and to clear debris from the airway. Steroids, antibiotics, and mechanical ventilation may be required.

In conclusion, the special complications associated with the use of endotracheal tubes during endoscopic laser surgery include the following: (1) tube ignition; (2) a metallic wrap placed around the tube may become torn and aspirated, producing airway obstruction; (3) pledgets or cottonoids used to protect the cuff may ignite or be aspirated; (4) trauma to the cords and airway can be produced, especially if the tube is metallic; and (5) laryngeal papillomatosis can be seeded more distally during passage of an endotracheal tube through the larynx. The commonest disturbance produced by an endotracheal tube during laryngeal surgery relates to the fact that the tube will lie in the posterior commissure of the larynx (where the larynx is widest), obstructing the vision and access of the surgeon if the pathologic lesion being treated is in the same area. On the other hand, pathologic lesions located in the anterior part of the larynx may be easily approached by the surgeon while a small endotracheal tube rests in the posterior larynx.

Jet Venturi Ventilation

Another technique in airway management for endoscopic laser surgery employs a Sander's type venturi jet ventilator during the operative procedure. In 1967, Sanders²⁶ described the use of a jet injector to ventilate lungs during bronchoscopy. This led to the application of jet injector ventilation techniques (based on the Venturi principle) for microlaryngeal procedures.²² Oxygen is delivered through a high-flow jet stream that entrains air, decreasing the FIO_2 while expanding the

tidal volume. Venturi ventilation may be accomplished using either a Carden tube,⁴ a Benjamin tube,¹ a cricothyroid catheter,³ or the operating laryngoscope.²² The Carden tube is a short, cuffed endotracheal tube that lies completely below the vocal cords. Jet ventilation is provided by a small catheter connected to this tube that delivers oxygen to the trachea with minimal obstruction of the surgical field. The Benjamin tube is a modification of this device, with the ventilating tube connected to a mushroom-type adapter in order to keep the ventilating tube in the middle of the tracheal lumen. Ventilation through a cricothyroid catheter is usually considered radical and is employed as a last resort technique if the laryngeal and subglottic areas are too diseased to permit acceptable ventilation through the larynx. Ventilation with any of these techniques has the risk of producing barotrauma to the tracheobronchial tree and lungs if the airway does not remain patent. For example, if these ventilating catheters lie distal to a closed glottis (due to laryngospasm or an obstructing laryngeal lesion), the high-pressure oxygen jetted to the trachea will produce high airway and pulmonary pressures.²⁰ Thus, these techniques necessitate paralysis to prevent laryngospasm and the assurance that laryngeal pathology does not interfere with escape of the jet ventilation gases from the tracheobronchial tree.

On the other hand, venturi ventilation through an operating laryngoscope less likely produces barotrauma and enjoys more frequent usage for jet ventilation in the operating room. The great advantage of this method is that the patient can be ventilated without an endotracheal tube and without any obstructing equipment in the larynx. When used properly, it affords unparalleled access to the laryngotracheobronchial tree for both diagnosis and surgery. A stream of oxygen is directed via various sized needles or tubes within the open lumen of the laryngoscope or bronchoscope. On the newer Jako suspension laryngoscopes we have replaced one of the two light sources with a metal surgical suction tube used as an injector tube through which venturi ventilation is accomplished. At high velocity, the jet oxygen stream is directed down the lumen of the instrument, entraining room air through the open end of the laryngoscope (the Venturi effect). This delivers a larger volume of oxygen-air to the respiratory tree under readily adjustable pressures allowing for adequate ventilation.

Because the jetted air enters the tracheobronchial tree from above the larynx, barotrauma with this system is far less likely. Should laryngospasm or a tumor mass obstruct the larynx, barotrauma due to lack of escape of ventilated gases would be unlikely; rather, inadequate ventilation would be observed. Adequacy of ventilation is assessed by looking at movement of the chest and listening to breath sounds. In addition, pulse oximetry and occasional arterial blood gas analyses document adequate oxygenation and ventilation. Utilizing a reducing valve, oxygen pressure supplied from a wall oxygen source is decreased to make inflation pressures safe (20 to 25 psi). Using a paint gun spray controller or another form of toggle switch, ventilation may be intermittently accomplished. With each jet of 100 per cent

oxygen, room air is entrained so that the FIO_2 is less than 100 per cent. In general, for any given oxygen pressure applied, the larger the airway, the larger will be the tidal volume but the lower will be the FIO_2 .¹⁷ The laryngoscope and larynx must be properly aligned so that jetted ventilation will travel through the laryngeal opening to provide optimal ventilation.

Reported complications of venturi jet ventilation include *pneumomediastinum* and *pneumothorax*.⁸ Although these may result from very high airway pressures mistakenly delivered to the tracheobronchial tree during jet ventilation, they usually result from a tear in the mucosa of the larynx or trachea created by a misdirected laser beam. Subsequent jet ventilation then allows dissection of air along tissue planes. It is therefore essential that oxygen pressure utilized during jet ventilation be limited by using a reducing valve. *Gastric distention* and *regurgitation* may result from delivery of air to the stomach during induction of anesthesia or by an incorrectly directed endoscope resulting in venturi ventilation of the esophagus, rather than ventilation of the trachea. *Ball valve phenomena* occasionally result during venturi ventilation when the air injection dilates the trachea, allowing inspiration of air past a polyp or mass, which then obstructs the tracheal lumen during expiration, resulting in inadequate expiration and pulmonary distention. *Vocal cord motion* occurs during the jet blast. To alleviate this problem, frequent inspiration with minimal delivery pressures may be employed. In addition, a rhythmic ventilation pattern assists the surgeon in synchronizing respiration with application of the laser. Also, many surgeons prefer to laser in a quiet field during apneic oxygenation. With this technique, very rapid jet ventilation is provided that is then interrupted by pauses in ventilation during which the surgical laser beam is employed. *Mucosal dehydration* may result from inspiration of nonhumidified air and carries the risk of increased postoperative laryngeal web formation. Techniques reducing this risk include the administration of steroids, good systemic hydration, and postoperative humidification of inspired gases. *Particulate blasting* of dissected tissue and blood down the tracheobronchial tree is possible during venturi ventilation but is less likely when the surgical technique employs laser excision because much of the dissected tissue is vaporized. *Hypoventilation* is always a consideration with venturi ventilation. The anesthesia team must constantly observe chest wall movement and breath sounds during inspiration and expiration and produce adequate relaxation to minimize cord movement and resistance to ventilation. For maximum ventilation, the tip of the laryngoscope is best placed close to the vocal cords and the axis of the laryngoscope should be the same as the tracheal axis to avoid "baffling" of the venturi effect. Frequently, ventilation becomes inadequate when the laryngoscope is misdirected, which also makes esophageal ventilation more likely.

Anesthetic Management

Preoperative Evaluation. Because many patients undergoing these types of surgical procedures have impaired airways or airway

obstruction, close attention must be paid to the status of the airway preoperatively. The degree of airway obstruction, adequacy of ventilation, and potential difficulty of laryngoscopy and tracheal intubation must be assessed. The quality of the patient's voice and respiratory pattern may provide information regarding airway obstruction. Preoperatively, fiberoptic laryngoscopy or bronchoscopy, computed tomography, and magnetic resonance imaging may assist in airway evaluation. Narcotic and sedative premedicant drugs should be avoided when there is a history of airway obstruction or apneic spells. In general, patients should be lightly premedicated, if at all, because rapid recovery of laryngeal reflexes and spontaneous ventilation is desirable at the conclusion of surgery. Preoperative or intraoperative administration of an antisialogogue, such as atropine or glycopyrrolate, minimizes airway secretions and facilitates airway visualization by both the anesthesiologist and surgeon.

Intraoperative Management. In adults with an adequate airway and after application of appropriate monitors and obtaining intravenous access, anesthesia may be induced with intravenous barbiturates. Dexamethasone, 0.2 mg per kg, may be administered intravenously following induction of anesthesia to decrease laryngeal edema postoperatively. In addition, all patients who do not receive an antisialogogue preoperatively receive glycopyrrolate, 3 μ g per kg, intravenously. The eyes are taped shut and covered with saline-moistened sponges.

If jet venturi ventilation is elected for airway maintenance intraoperatively, anesthesia induction includes a hypnotic agent, provision of a good airway and then succinylcholine, 1.5 mg per kg, and lidocaine, 1.5 mg per kg intravenously, following which the table is turned 90 degrees for surgical access. Surgical laryngoscopy and venturi ventilation are initiated with the latter controlled at a frequency of 20 to 30 times per minute with an inspiratory/expiratory ratio of approximately 1:1.

Our preference is to maintain anesthesia by infusion of a short-acting opioid, such as alfentanil administered at 0.75 to 1.5 μ g per kg per minute, supplemented with bolus doses of thiopental as needed. On the other hand, if a barbiturate infusion is employed for maintenance of anesthesia, then administering fentanyl or another short-acting narcotic is beneficial in reducing the stress response during this very stimulating surgical procedure. During laser surgery patient movement must be kept to a minimum, because patient movement of any type may cause the laser beam to strike and damage normal tissue or ignite flammable materials in the field. Therefore, most clinicians choose to employ a deep anesthetic technique supplemented by profound muscle relaxation. Relaxation is provided by a succinylcholine drip or alternatively by one of the newer short-acting nondepolarizing agents, such as atracurium or vecuronium. At the completion of the endoscopic procedure, the table is again turned 90 degrees for better control of the airway and lidocaine, 1 to 1.5 mg per kg, may be administered intravenously to facilitate emergence without laryngo-

spasm. The use of an endotracheal tube allows maintenance with halogenated agent, O₂, and air mixtures.

Young children are managed in a similar fashion, with the exception that anesthesia is induced by mask inhalation of halothane or another inhalational agent. Uncooperative children may be induced with intramuscular ketamine or rectal brexital (10 per cent solution, 25 mg per kg). If an endotracheal tube is employed, the same induction regimen is employed. The tube is inserted, correctly positioned, and secured prior to turning the table and allowing surgical laryngoscopy to begin.

Special precautions for endoscopic laser procedures include the fact that before anesthesia is induced in patients with critical airways, a surgeon experienced in performing tracheostomies must be present and *all* equipment, including the laser, should be available and in a ready state. Appropriate bronchoscopes, suction, and so forth must be in readiness. A pulse oximeter proves to be especially useful in these procedures, particularly when room lights are dimmed in order to continuously assess adequacy of oxygenation. Another useful monitor is the video screen image. This is a TV screen that reproduces the image seen by the surgeons through an operating microscope, so that anesthesiology and operating room personnel can view the same operating field. In my experience, this is especially useful in paralyzed patients because it provides observation of vocal cord movement during the early return of laryngeal muscle function, prior to the observation of a muscle twitch or train-of-four on the peripheral nerve stimulator. Postoperatively, if laryngeal edema or a croupy cough develops in the postanesthesia care unit, racemic epinephrine (Micronefrin) may be of advantage. A dose of 0.2 ml of 2.5 per cent solution is diluted in 5 ml H₂O and then delivered to the patient through a raindrop nebulizer powered by a wall oxygen flowmeter.

SUMMARY

Endoscopic laser surgery offers the surgeon new capabilities in treating airway disease. Laser devices now come in a variety of forms, with newer technology offering fine tuning for different surgical applications. Specifically, endoscopic laser surgery allows the surgeon access to the field without any kind of obstructive instrumentation. However, this new technology offers anesthesia practitioners new challenges. How does one share the patient's airway with the surgeon, protect that airway, and offer adequate anesthesia while not obstructing surgical access to the operating field? Most commonly, the patient's airway is protected by employing either a metal endotracheal tube or a modification of currently available endotracheal tubes in order to reduce the likelihood of laser-induced endotracheal tube fires and other complications. In addition, Venturi jet ventilation through an operating laryngoscope allows entrainment of an oxygen-air mixture for patient ventilation while minimizing any kind of foreign object

in the surgical airway. As has been detailed in this article, there is no perfect anesthetic management technique available. Every new modification offers subtle advantages and differences over techniques previously available but also has one or more unwanted complications associated with its use. The safe anesthetic management of the patient undergoing endoscopic laser surgery requires considerable agility and flexibility by the anesthesia practitioner in order to adapt to rapid changing surgical needs and to provide a safe anesthetic for a patient undergoing a somewhat complicated surgical procedure. As someone once said, vigilance takes on new meaning when describing the anesthetic management techniques of patients undergoing endoscopic laser surgery.

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Spinal Cord Injury

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Currently, 10,000 patients with spinal cord trauma survive the initial injury to arrive at our nation's hospitals annually³⁹; 70 per cent of these patients are 19 to 34 years old.¹⁸ The mortality rate following hospital admission is 5 to 12 per cent within the first 3 to 12 months. Therefore, despite an approximate preadmission mortality rate of 50 per cent,⁴³ the population of long-term survivors of this injury continuously expands.¹⁸ In spite of continuing disagreement on the advisability of surgical intervention, 78 per cent of patients with acute spinal cord injury admitted to one center had some type of surgical procedure.⁷⁹ Patients in the chronic phase of the injury often require multiple surgeries, especially urologic and plastic procedures. Additionally, the anesthesiologist may have to care for an occasional patient with a spinal cord lesion who is in labor.

The physiologic sequelae of spinal cord injury are severe, both in the acute and chronic phase of the injury. The respiratory, cardiovascular, neuromuscular, temperature regulatory and genitourinary, digestive, hematopoietic, and fluid and electrolyte systems, among others, are commonly involved. We will discuss the current concepts of the pathophysiology of spinal cord injury, review the experimental and clinical modalities of spinal cord resuscitation aimed at preservation and restoration of useful function, and focus on the medical implications of spinal cord damage and how they influence anesthetic management.

PATHOPHYSIOLOGY

The initial injury to the spinal cord may produce immediate functional or anatomic disruption. The extent of destruction of the cord

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relates to the severity of the traumatic force. Severe injuries lead to direct neurilemmal and neuronal disruption or destruction, petechial hemorrhages, gross hematomyelia, or even a total cord transection, a rare event. The damage in these areas will progress to a cavitating necrosis and ultimately to glial scar formation. In less severe injuries, the central gray matter is damaged first; changes in the white matter follow. The loss of white matter accounts for the clinical picture of paraplegia or quadriplegia.

The observation of progressive changes within the injured spinal cord has led to the concept of a secondary injury, perhaps mediated and propagated by mechanisms distinct from the initial mechanical deformation. The extension of the initial gray matter lesion to the white matter is preceded by vascular endothelial damage with platelet adhesion, aggregation, occlusion of the microvasculature, and embolization with microthrombi.

On a macroscopic scale, vascular stasis, decreased spinal cord blood flow (SCBF), and ischemia are noted. Axonal degeneration (hydropic and then granular), myelinolysis, cell necrosis, inflammatory infiltrate, and neuronophagia ensue. A striking feature is the occurrence of intra-axonal calcium hydroxyapatite crystals and mitochondrial calcification. Similar degenerative changes have been observed following *in vivo* exposure of rat spinal cords to calcium or calcium in the presence of an ionophore.⁴

Biochemical events coinciding with this process of progressive autodestruction include (1) a massive translocation of calcium from the extracellular to the intracellular space; (2) decreased Na^+K^+ -ATPase activity; (3) the loss of intracellular potassium; (4) activation of phospholipase A_2 leading to arachidonic acid release and its metabolism to lipid peroxides (via free radical attack), prostaglandins (via cyclo-oxygenase), or leukotrienes (via lipoxygenase); (5) increase in total thromboxane A_2 , as well as its ratio to prostacyclin; (6) the degradation of axonal and myelin proteins by neutral proteinases; (7) the failure of energy metabolism and protein synthesis; and (8) hypoxia and lactic acidosis.^{2, 4} The tantalizing aspect of this wealth of biochemical data is that it is possible to organize these events into a positive feedback cascade mechanism activated by the release of certain catalysts from the blood and their initial intracellular flux caused by the endothelial and neuronal membrane disruption at the initial site of maximal tissue trauma. Calcium,³⁶ in addition to bradykinin, thrombin, and ferrous ion,² has been cast in such a role. Another recent investigator⁴⁸ made a case for norepinephrine.

The basic scheme of a secondary injury is hypothesized to follow activation of membrane phospholipase A_2 , which yields arachidonic acid, lipid peroxides, free radicals, prostaglandins (mostly thromboxane), and leukotrienes. These can account for membrane lipid destruction, microcirculatory thrombosis and stasis, vasogenic edema, ischemia, and chemotaxis. Calcification of mitochondria and other intracellular sites secondary to influx of Ca^{2+} through damaged membranes should have obvious deleterious effects on cellular energy me-

tabolism and maintenance of integrity and function. $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity has been shown to be phospholipid dependent and very susceptible to free radical attack and lipid peroxidation.⁴⁸ This enzyme is needed to maintain normal cellular volume and ion content, membrane potential, and cellular function. Finally, the neutral proteinase, which is the predominant source of increased proteolytic activity in experimental spinal cord injury, is activated by calcium.⁴

The feasibility of these secondary injury mechanisms is supported by a number of additional observations. The time course of change in tissue concentration of the various proposed mediators closely matches that of the histologic, biochemical, and physiologic processes described previously. In the case of calcium, neurologic deficit scores have also been shown to be proportional to the extent of calcium influx, the rise in phospholipase-generated metabolites, vascular damage, and increased tissue water content.³⁷ In addition, as mentioned previously, exposure of the spinal cord to calcium chloride solution results in similar prostaglandin (thromboxane) generation, proteolysis, and morphologic changes in proportion to the solution molarity.³⁶ Moreover, the intracellular calcium influx may be further increased by the release of glutamate and aspartate, which are excitatory neurotransmitters with well-documented neurotoxic properties. Recently, Faden and Simon²² have shown improved neurologic outcome in rats subjected to thoracic cord injury treated with MK-801, an N-methyl-D-aspartate (NMDA) glutamate-receptor antagonist.

In a different study, Faden's group²¹ demonstrated an increase in the endogenous opioid kappa receptor agonist, dynorphin, as well as an increase in receptor-binding capacity after experimental spinal cord injury in rats. These findings correlated closely with the degree of neurologic dysfunction. No change in mu or delta receptor binding was found. Because intrathecal dynorphin A, but not other opiate agonists, can produce dose-related hind-limb paralysis in the rat, it has been postulated that this opioid system may contribute to the pathophysiology of secondary spinal cord injury.^{21, 44} However, in many such experimental models, caution must be exercised in equating close correlation with causation, and further investigation is necessary. The fact that the secondary sequence of events may not begin for over an hour, and in some cases as much as 4 hours after the primary injury, suggests the possibility of pharmacologic intervention to prevent or alter the resulting ischemic sequence.⁶⁷

The normal mean spinal cord blood flow of 40 to 50 ml per 100 g per minute is partitioned in a ratio of 3:1 between gray and white matter, respectively.⁶⁴ Autoregulation of SCBF between mean pressure values of 60 and 150 mm Hg has been demonstrated in dogs.²⁷ SCBF has been shown to vary in direct proportion (1:1) with PaCO_2 .²⁸ Regardless of the biochemical or physiologic mediators involved, what has been clearly documented is that in the period following primary spinal cord injury, a progressive decrease in SCBF occurs, resulting in marked ischemia associated with a morphologic and biochemical cascade as detailed previously. Although conflicting results have been

reported,⁴¹ the preponderance of researchers agree that total SCBF decreases significantly from 1 to 4 hours after subtotal experimental injury, with most of the decrease occurring in the central cord region.⁶⁵

Spinal cord injury in cats will abolish autoregulation with the onset of ischemia.⁶⁸ This derangement renders the spinal cord susceptible to increased hemorrhage and edema in the face of significantly increased blood pressure, as has been shown experimentally in cats.⁶¹ Such a hypertensive phase has been documented for 3 to 4 minutes after experimental spinal cord injury.^{62, 80} Spinal shock, in which endorphin-mediated parasympathetic stimulation has been implicated, would decrease SCBF in the absence of autoregulation.

Also, vasoconstriction of resistance vessels would more readily result in ischemia. Such vasoconstriction may be secondary to some of the mediators already mentioned: a preponderance of thromboxane over prostacyclin, PGF₂ alpha, and slow reacting substance of anaphylaxis.² Although the originally proposed increase in spinal cord catecholamines (as a cause of ischemia and hemorrhagic necrosis)^{57, 58} has not been verified by subsequent investigators, norepinephrine has been shown to significantly reduce SCBF when the cord-blood barrier has been disrupted.¹¹ More recent investigations already mentioned have enumerated a number of membrane-damaging factors, operating by way of free radical attack and lipid peroxidation, which may disrupt the cord-blood barrier and which correlate with cord edema. Norepinephrine has been shown to be capable of activating similar membrane lipid peroxidation.⁴⁸ Of interest is the finding that acute ethanol intoxication (blood level of 100 mg per dl) worsens spinal cord hemorrhage, increases the extent of anatomic damage, and impairs recovery of function.³

On a gross physiologic scale, spinal cord impulse transmission, as assessed by evoked potentials, disappears immediately with complete transection and after a variable delay period in less severe lesions. Somatosensory-evoked potentials (SSEPs) studied in humans distinguished complete anatomic lesions with little or no hope of recovery from patients with complete or incomplete functional deficits, but could not predict the degree of functional deficit.⁹ On the other hand, motor-evoked potentials (MEPs) or corticomotor-evoked potentials (CMEPs) have been shown in both rat and cat dynamic spinal cord injury (SCI) models to be more sensitive indicators of the onset of injury,⁵⁰ as well as good predictors of the extent of tissue damage and prognosis for functional recovery.^{51, 69}

RESUSCITATIVE MODALITIES

A number of pharmacologic and physical measures have been employed in an effort to limit the progression of secondary SCI and, it is hoped, to yield improved neurologic recovery. Because spinal cord injury may abolish autoregulation, causing SCBF and blood volume to vary directly with blood pressure, perfusion pressure must be

maintained close to the middle of the normal autoregulatory range (60 to 150 mm Hg) by cautious restoration of circulating blood volume (see Cardiovascular Complications in this article). In addition, glucocorticoids and hyperosmolar agents have frequently been used to decrease post-traumatic edema and increase SCBF. Cyclooxygenase and proteinase inhibitors, vasodilators, antioxidants, calcium channel blockers, and NMDA glutamate receptor antagonists have been studied, but, in view of the limited experimental and clinical work to date, they will not be reviewed in detail.

Mannitol draws fluid from the interstitial space into the intravascular space and then promotes a net loss of fluid via osmotic diuresis. It reduces edema following traumatic canine spinal cord injury.⁵⁹ Because of initially low central venous pressures (in the acute phase after SCI) and an impaired cardiac reserve, allowance must be made for the increase and then decrease in venous return caused by mannitol.

In a canine model, improved functional recovery after SCI has been demonstrated with dexamethasone therapy.⁴⁵ Better recovery of SSEPs and partial restoration of extracellular calcium concentration have been shown in cats receiving 15 to 30 mg per kg of methylprednisolone 45 minutes after spinal cord contusion.⁸¹ Others have found less axonal degeneration using morphometric analysis when the same steroid dose was given to rats after SCI.³⁸ Nonetheless, the multicenter, double-blind, randomized clinical trial in humans sponsored by the National Acute Spinal Cord Injury (NASCI) Study Group failed to find any improvement in motor or sensory neurologic function 1 year after injury as a result of two levels of methylprednisolone therapy.⁸ The authors make several cautionary comments regarding interpretation of this study. First, animal studies may not accurately duplicate conditions of human SCI, not to mention interspecies differences in anatomy, physiology, or biochemistry. Second, both study doses of methylprednisolone were below the 15 to 30 mg per kg range used in the most successful animal studies. Third, there was no placebo control group; the two steroid regimens were compared with each other and then with historical outcome data. Finally, only 12 per cent of the patients started treatment within 3 hours of injury and another 20 per cent between 3 and 6 hours after injury; the remainder entered the study up to 48 hours after their injury. These deficiencies mandate further investigation of the usefulness of steroids, especially larger doses given earlier.

It should be noted that the NASCI study excluded patients with severe associated injuries. Spinal-cord-injured patients with severe multiple trauma have more than a threefold increase in infections, which often involve multiple organisms and foci, when receiving steroid therapy for CNS trauma (4 to 20 mg of dexamethasone every 6 hours). All deaths resulting from sepsis occurred in steroid-treated patients.¹³ In patients with SCI and severe multiple trauma, it would seem wise to avoid steroid treatment.

The area of opiate antagonist therapy is currently a subject of heated research and debate. Following the demonstration that the

opiate antagonist naloxone improved arterial pressure and survival in hemorrhagic and septic shock, investigators studied its effect in spinal shock and in enhancing recovery from spinal cord injury.³² Intravenous naloxone has effectively prevented or reversed spinal shock in rat and cat cervical cord transection models, significantly increasing mean arterial pressure (MAP), increasing respiratory rate, and decreasing hypothermia.^{34, 35} Also, naloxone in doses of 2 to 10 mg per kg has been shown to yield significant improvement in SSEPs²³ and neurologic function.²⁰

Although these and many other animal studies supported naloxone's effectiveness, a human phase I clinical trial of naloxone was less encouraging.²⁴ This trial showed some clinical improvement only with the highest loading dose of 5.4 mg per kg (IV) followed by a continuous hourly infusion of 75 per cent of this amount for 23 hours. However, the results fell short of statistical significance. The mortality rate was not greater than expected in similar injuries, but awareness of pain was significantly increased. A possible factor limiting the success of naloxone, could be the average interval of 6.6 hours from admission until initiation of therapy.²⁴ Although further clinical trials are needed, a number of recent animal researchers challenge the effectiveness of naloxone.^{31, 75, 76} In fact, a recent case report⁵ underlines a potentially deleterious effect of naloxone therapy in patients undergoing general anesthesia. A patient received 5.4 mg per kg of naloxone 30 minutes before presenting for stabilization of the thoracolumbar spine. Fentanyl (25 μ g per kg), isoflurane (2 to 3.5 per cent), thiopental (700 mg), diazepam (10 mg), morphine (15 mg), and sufentanyl (0.5 μ g per kg) were required during and immediately after surgery to manage hypertension and hyperventilation. This resistance to normally effective anesthetic doses was attributed to an antianalgesic and analeptic effect of the naloxone treatment.⁵

Experimental work on the possible sites and mechanisms of action of opiate antagonists has been reviewed.³² Briefly summarized, evidence indicates that naloxone interacts stereospecifically at a central site to inhibit opiate receptor-mediated stimulation of the parasympathetic nervous system in achieving improvement of MAP and SCBF. A central outpouring of beta endorphin following SCI has been found at the time of cord ischemia, and naloxone may antagonize its effects. In addition, naloxone elevates peripheral dopamine levels by 300 to 400 per cent, partially contributing to naloxone's hemodynamic effects after SCI. Other catecholamine levels remain unaltered. Finally, because naloxone is only effective in doses many times greater than that required for mu-receptor agonist reversal, it is possible that its effect in SCI occurs at a receptor, perhaps the kappa receptor, for which it has marginal affinity. Naloxone and a specific kappa-receptor antagonist have prevented experimental cord damage induced by dynorphin, a kappa-receptor agonist (see previous discussion). In fact, some evidence exists that naloxone acts through nonopioid mechanisms, involving its ability to inhibit membrane damage by free-radical-in-

duced lipid peroxidation, to act as an antioxidant, to modulate calcium fluxes, and to increase cyclic-AMP activation of prostaglandins.

Recent studies have demonstrated potential effectiveness of GM-1 ganglioside⁷ and a combination of triethanolamine and cytosine arabinoside³⁰ to markedly stimulate axonal growth in rats with transected spinal cords. Continuously applied weak electrical fields achieved similar results in guinea pigs.⁶ A series of investigations demonstrates that peripheral nerve grafts or CNS implants derived from the embryonal neuraxis can stimulate axonal outgrowth and may prove useful in repairing disrupted intraspinal circuits.⁶³

Currently, much of this work has proven to be a limited clinical utility. Nevertheless, understanding and new directions for research, as well as more effective application of existing knowledge, are advancing at an unprecedented and encouraging pace. Prompt initiation of currently accepted therapy or experimental protocols in a specialized care center holds the most hope for preserving or restoring function.

MEDICAL IMPLICATIONS

Respiratory Complications

Depending on the level and degree of spinal cord injury, respiration may be impaired by paralysis of abdominal, intercostal, diaphragmatic, and accessory muscles of respiration, progressively, as the site of trauma moves from low thoracic to high cervical or even brainstem levels. Loss of motor function originating at C₃ to C₅, the origin of the phrenic nerves, results in diaphragmatic paralysis (major contribution from C₄). High quadriplegia (C₄ or above) results in a severe, life-threatening decrease in all standard measures of respiratory mechanics and dynamics: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), peak inspiratory and expiratory force and flow, and total pulmonary compliance. Only the accessory muscles of inspiration (sternocleidomastoid, scalenes, and trapezius) function during inspiration. Lower rib cage and abdominal paradox is seen as the hemidiaphragms passively respond to the changes in intrathoracic pressure caused by accessory muscle activity. As the upper rib cage expands (less than with intact intercostal muscles), upward diaphragm motion decreases intra-abdominal pressure, resulting in inward movement of it and the lower rib cage. The reverse occurs during expiration. The paradoxical diaphragm motion decreases the efficiency of already diminished muscle activity in effecting air flow.⁵² Tidal volume, inspiratory and expiratory reserve volumes (IRV and ERV), and functional residual capacity (FRC) are critically reduced, whereas residual volume is increased.¹⁵

Alveolar hypoventilation results in hypercarbia. Hypoventilation, atelectasis, and airspace collapse, associated with the decrease in FRC relative to closing volume, produce ventilation-perfusion (V/Q) mis-

matching, leading to hypoxemia. In this case, respiratory function is worst in the supine or Trendelenburg position, as abdominal contents displace the diaphragm further cephalad, and improves if other variables (for example, blood pressure) permit elevation of head and thorax. Global hypoventilation often deteriorates further during sleep, occasionally progressing to sleep apnea, which has been attributed to diminished CO₂ responsiveness.^{12, 33}

Low quadriplegic patients with partial or complete integrity of diaphragmatic innervation will have variable diaphragmatic function, but, the diaphragms are prevented from achieving their optimal, steeply domed fiber length-tension position at end-expiration because of intercostal and abdominal muscle paralysis; hence, their inspiratory efficiency is impaired. *Inward* motion of the upper rib cage during inspiration adds to this effect (cf. lower rib cage and abdominal paradox in high and quadriplegics).⁵³ Forner and others²⁶ studied flow-volume loops in such patients at 5 months post-injury, noting a 50 per cent decrease in FVC and decreased peak expiratory and inspiratory flow. Decreases in expiratory flow were much less at low lung volumes (at 25 per cent of total body capacity, flow was 72 per cent of the predicted value) than at higher lung volumes (55 per cent of predicted). This finding implicates muscle weakness rather than intrinsic airway disease, airway compression, or decreased lung compliance as the primary cause of the decreased flow rates. Normally, initial expiratory flow rate is effort dependent, whereas late expiratory flow rates are effort independent and are limited by airway compression, which increases resistance proportionately to thoracic pressure. Muscle weakness, therefore, would decrease end-expiratory resistance. Trendelenburg position, by shifting the diaphragms cephalad to a more mechanically advantageous starting fiber length, actually increase IRV and FVC an average of 300 ml.²⁶

Low quadriplegics and paraplegics are still at risk for hypoventilation, V/Q mismatching, and retention of secretions, with results as outlined previously. Aside from diaphragmatic and intercostal muscle strength, a key factor in overall respiratory function is the contribution of the abdominal muscles in increasing expiratory pressure directly, as well as improving the efficiency of the intercostals in forced expiration or coughing by preventing paradoxical movement of the diaphragm into the abdomen. The absence of abdominal muscle function accounts for the persistence of respiratory complications, especially retained secretions and pulmonary infections seen in some paraplegics with intact diaphragms and intercostal muscles.

Any comatose, apparently apneic, or cyanotic patient, or those unable to manage their secretions should receive endotracheal intubation as soon as possible. Also essential, immobilization of the spine prevents extension or completion of an incomplete lesion. In cervical injuries, the head should be maintained in the neutral position (neither flexed nor extended) by *gentle* traction (the aim is *not* reduction) so as to avoid neck movement during intubation. Blind nasotracheal intubation, as well as laryngoscopic or flexible bronchoscopic oral or

nasal intubation, are all possible and should be chosen on the basis of the ability to accomplish the task both as quickly as possible and without disturbing the existing cervical alignment. The distinct possibility of sinus arrest or complete heart block resulting from unopposed vagovagal reflexes following pharyngeal and tracheal stimulation in lesions above T₄ should be remembered and can be prevented by 0.6 mg of atropine administered intravenously.⁷⁸

No mode of mechanical ventilation is superior in terms of patient outcome. However, synchronized intermittent mandatory ventilation and variable pressure support ventilation offer the advantages of enhanced venous return and tailored respiratory muscle exercise when compared with controlled ventilation. Where indicated, positive end expiratory pressure (PEEP) will normalize FRC, reduce shunting, and increase compliance.

Respiratory complications are the most common cause of death in acute SCI, with pneumonia being the second most important cause (after anoxic death at the time of injury).⁷¹ In chronic, stabilized patients, respiratory infections decrease in frequency and cause less than 10 per cent of febrile episodes. The importance of aggressive pulmonary toilet in addressing this problem was evidenced by a 33 per cent decrease in prolonged ventilation resulting from such measures as careful monitoring of pulmonary function, vigorous chest physical therapy, and early bronchoscopy with lavage if lobar collapse developed on chest roentgenograph.⁵⁵ Any fever accompanied by leukocytosis, physical, and/or radiographic evidence of pneumonitis warrants aggressive treatment.

Cardiovascular Complications

The hemodynamic sequelae of SCI follow a sequential pattern beginning at the moment of injury. First, for 3 to 4 minutes following spinal cord compression, a sudden drastic increase in systolic blood pressure, to 200 to 250 mm Hg, occurs in laboratory animals.⁶² This has been attributed to an early thoracic sympathetic outflow and, later, adrenally mediated secretion of catecholamines.⁸⁰ The possible role of this abrupt pressor response in augmenting the extent of hemorrhagic necrosis and releasing possible mediators of secondary injury is discussed in the section on pathophysiology.

Experimental cord injury has been shown to result in transient but significant increases in intracranial pressure, blood-brain barrier permeability, brain water, and extravascular lung water with a marked decrease in cerebral blood flow.¹ This study by Albin and colleagues¹ also noted the severe increase in blood pressure (to a mean of 225 mm Hg), lasting for 6 minutes, and additionally reported increases in pulmonary artery pressure, pulmonary capillary occlusion pressure, central venous pressure, and cardiac output. Of note, the intracerebral and pulmonary changes occurred before the full development of the cardiovascular changes. This finding, along with the fact that phenolamine pretreatment prevented the cardiovascular changes but did not prevent the brain and lung events, seems to support independent

but causally linked mechanisms as the etiology of both processes. At any rate, this work is compatible with the clinically observed susceptibility to pulmonary⁵⁶ and cerebral edema seen during resuscitation of spinal-cord-injured patients, and it reinforces the advisability of early hemodynamic monitoring to guide fluid management in these individuals.

Because SCI patients rarely reach medical attention within minutes of their injury, acute hypertension is rarely, if ever, observed. Most patients present with varying degrees of shock, which features hypotension, bradycardia, decreased total peripheral resistance, low or normal central venous pressure, and normal or elevated cardiac output.⁵⁶ Orthostatic and other pressor reflexes are diminished or absent, and thermoregulation is lost. At the same time, somatic and visceral motor and sensory loss below the level of the lesion is observed. The extent of these changes relates to the level of the cord injury. Injuries at or above T₁ may result in mean blood pressures as low as 40 mm Hg. The observed bradycardia may be due to unopposed vagal tone secondary to loss of the cardiac accelerator fibers (T₁ to T₄), but many feel that the Bainbridge reflex, caused by a fall in right atrial and central venous pressures, is a more important contributing factor, as bradycardia can occur with lesions below T₄. The critical level above which significant hypotension will be manifest is T₆ to T₇.

This phase of spinal shock may last days to weeks but is more abbreviated than the period of flaccid paralysis of skeletal muscle. Unfortunately, no one has delineated the point at which the sympathetic neurons regain their functional ability, now autonomous from higher control; but, it is clear that they do regain some tonic activity as well as the ability for reflex reaction as evidenced by the unpredictable onset of potentially catastrophic sympathetic reflex spasticity.

Alterations in cardiovascular function during the subacute and chronic phases of SCI feature the persistence of a slightly low to normal blood pressure and pulse rate in most patients, punctuated by episodes of severe hypertension in up to 85 per cent of those with lesions at or above T₆. These hypertensive spasms are triggered by day-to-day stimuli, most often distention of a hollow viscus, such as bladder or rectum. Other stimuli, including temperature extremes, contractions of labor, or surgery, may be particularly potent.⁴⁹ The tendency toward reflex hypertension is called autonomic hyperreflexia. Its symptoms include facial paresthesias, nasal congestion, severe headache, dyspnea, nausea, and blurred vision. Typical diagnostic signs are vasoconstrictive pallor, sweating and piloerection below the level of the lesion,⁴⁰ vasodilation and flushing above the lesion site, which are accompanied by bradycardia and severe hypertension.¹⁴ Subarachnoid and retinal hemorrhages have been observed, and syncope, convulsions, and finally death can occur if hypertension continues unabated.⁴⁹

The neuroanatomic correlates of this syndrome include stimuli arising from somatic or visceral receptors, causing afferent impulses that follow their normal course via the posterior columns and spi-

nothalamic tracts. Spinal cord section prevents these impulses from reaching the brain, but they do synapse with cells of the intermediolateral gray matter, giving rise to efferent sympathetic discharges. Normally, these reflexes are localized in nature, but after SCI they tend to involve most of the sympathetic system below the level of the lesion. The usual homeostatic inhibitory impulses from higher centers, which in normal conditions follow the initial arrival of the afferent impulses, never reach the cord below the lesion. Intense, unabated somatic and visceral muscle contractions, arteriolar spasm, sweating, and piloerection are caused by the unchecked sympathetic reflexes below the cord lesion. Above the cord lesion, the hypertension caused by the arteriolar spasm and adrenal secretion activates carotid sinus and aortic arch baroreceptors as well as other CNS reflexes to cause vagally induced bradycardia as well as generalized vasodilation. These measures, however, are insufficient to prevent the hypertension when the lesion is above the origin of the splanchnic sympathetic outflow (T_4 to T_6). The time at which spastic autonomic or somatic reflex activity supercedes spinal shock and flaccid paralysis is difficult to predict and may occur 1 to 3 weeks or sooner after injury.¹⁴ Cardiac arrhythmias and electrocardiographic abnormalities may also contribute to cardiovascular risk in these patients. Acute, midthoracic spinal cord compression, besides producing hypertension, usually results in sinus or nodal bradycardia in monkeys.¹⁹ Moreover, this initial response often precedes the pressor response. The initial bradyarrhythmias are followed by premature atrial and ventricular contractions, atrioventricular dissociation, or ventricular tachycardias. Atropine prevents the bradycardia, whereas propranolol prevents the delayed ventricular tachyarrhythmias.¹⁹ The electrocardiogram frequently shows ST-T wave changes variously interpreted as left ventricular strain pattern or consistent with subendocardial ischemia.^{53, 60} Similar arrhythmias have been reported in 75 per cent of autonomic hyperreflexia episodes.⁴⁰ The potential for severe bradycardia, heart block, and even cardiac arrest pursuant to tracheal stimulation should generate concern and may necessitate intravenous atropine.⁷⁸

Management of these cardiovascular problems is dictated by the physiologic alterations that produce them. In the case of hypotension, a conservative approach is usually indicated, the urgency of treatment being proportional to the degree of hypotension and the symptomatology (CNS, cardiac, renal, and so forth) produced. Hypotension usually results from decreased venous return following sympathetic denervation, which causes increased venous capacitance. However, decreased cardiac reserve indicates cautious volume expansion. The decreased ability to accommodate excess volume is a natural consequence of the inability to further increase venous capacitance as the venous reservoir becomes full. Central venous pressure increases relatively little until the point when volume equals capacity and then rises abruptly. On the other hand, left ventricular and left atrial pressures increase proportionately with filling volume, and such indices as pulmonary capillary occlusion pressure provide an early and accurate

measure of volume status before central venous pressure finally rises equivalently. Furthermore, sympathetically mediated reflex increases in heart rate and contractility are not possible in the event of lesions above T₁.⁷³ Finally, the possibility of altered pulmonary capillary permeability to water during the acute phase of SCI may play a role in the observed susceptibility to pulmonary edema during resuscitation of these patients, as occurred in 44 per cent of patients in one series.⁵⁶

In view of these findings, the early use of pulmonary artery catheters in monitoring fluid resuscitation during spinal shock seems prudent. Not only are filling pressures and volume status readily assessable, but cardiac output and total peripheral resistance can also be measured and manipulated if they are found to contribute to hypotension.

MacKenzie and colleagues⁵⁴ outlined a relatively simple method of assessing cardiac function based on the response of PCWP and cardiac output to volume loading. If, in spite of volume loading, cardiac output and mean arterial pressure are such that spinal cord and other organ hypoperfusion seems likely, inotropic support is indicated. One study¹⁶ compared the efficacy of either dopamine or transfusion in raising mean arterial pressure and augmenting SCBF in rats. Both maneuvers improved these two variables, but transfusion alone was better than dopamine alone.¹⁶ The demonstration that naloxone-mediated increases in systemic blood pressure and SCBF may be mediated by increased endogenous plasma dopamine levels also suggests that this inotrope may be used where indicated without adversely affecting the potential for spinal cord recovery.³²

The prevention of autonomic hyper-reflexia during surgery and anesthesia has been successful. Schonwald and coworkers⁶⁶ reported a series of 219 patients with SCIs. Of the patients with lesions at or above T₅, 33 per cent underwent general anesthesia with halothane (37 cases) or enflurane (12 cases), and none of these developed autonomic hyper-reflexia or arrhythmias. Of nine patients in this group receiving nitrous oxide-narcotic anesthesia, two developed intraoperative hyper-reflexia. In 97 cases of spinal anesthesia with tetracaine, no attacks occurred, but one lidocaine spinal anesthetic apparently wore off before the end of urologic surgery, resulting in autonomic hyper-reflexia. The authors noted the level of injury as a major factor influencing the technical ease and feasibility of lumbar subarachnoid block, with low levels of injury resulting in failure in 3 of 19 patients, most likely as a result of previous spine surgery or traumatic distortion of the anatomy. Successes in preventing hyper-reflexia intraoperatively are not infrequently reversed by episodes occurring in the recovery room.

Genitourinary Complications

Acute renal failure, though uncommon, may occur in acute SCI patients as a result of hypotension, dehydration, sepsis, nephrotoxic drugs, acute obstruction, associated kidney trauma, and other influ-

ences. During the chronic phase of SCI, renal failure becomes a progressively more important cause of death, accounting for 20 to 75 per cent of mortality. Pyelonephritis, amyloidosis, and hypertension are the most commonly identified proximate causes of death.⁷¹

Urinary retention, more often a problem in the flaccid lower motor neuron bladder than in the spastic upper motor neuron type, predisposes the patient to autonomic reflexes and cystitis. Vesicoureteral reflux may result from this, as well as neurogenic causes. Repetitive ascending pyelonephritis occurs, leading eventually to secondary renal and adrenal amyloidosis and insufficiency. Neuropathic bladder outflow obstruction often contributes to the problem. Also, renal calculi tend to recur in these patients, and most often consist of the triple phosphate variety associated with urease-producing bacteria (for example, *Proteus* organisms). Some investigators feel that hypercalciuria may play a limited role.⁷¹ A large proportion of surgery in chronic SCI patients is devoted to cystoscopy, urologic invasive diagnostic studies, stone removal, lithotripsy, and urinary drainage or diversion procedures.

Urinary tract infections are a persistent problem. Prophylactic drug regimens have not been successful in substantially decreasing bacteriuria and bacteremia. Intermittent bladder catheterization seems to decrease infection rates, urolithiasis, and renal dysfunction when compared with indwelling catheterization, but requires considerable time and equipment. Conclusive prospective studies are lacking.⁷¹

Renal insufficiency causes disturbances of fluids and electrolytes, cardiovascular function, and other systems. Hyponatremia, hypoproteinemia, hypocalcemia, increased extracellular and total body water, hypertension, and congestive heart failure may all be caused or exacerbated. These aberrations, as well as altered drug clearance, are clearly of concern to the anesthesiologist; the avoidance of potentially nephrotoxic drugs is obviously advisable.

Therefore, careful preoperative evaluation of renal function is essential. Proteinuria usually constitutes the earliest sign of renal dysfunction, although the finding is qualitative rather than quantitative.⁷⁴ Serum creatinine may be misleading owing to the decrease in muscle mass seen in quadriplegics. Intravenous pyelography allows excellent visualization of the upper urinary tract, but significant functional impairment may precede detectable anatomic alterations. Renal scintigraphic determination of effective renal plasma flow seems to be a sensitive indicator of renal dysfunction and also correlates with the presence of renal calculi, altered renal architecture, and recurrent episodes of fever and chills.^{46, 47}

Sexual dysfunction is a usual finding in these patients. Males suffer from impotence and decreased or absent ability to achieve orgasm and ejaculation. Infertility occurs frequently, features abnormal spermatozoa, becomes more pronounced with higher lesions, and has no underlying endocrinological cause. Women experience altered sexual function on the basis of sensory and motor deficits, although normal menses usually resume within 1 to 3 months of the injury.⁷¹ Fer-

tility seems to be unimpaired, and if pregnancy occurs, premature labor and delivery are more common. Sensory loss above T₁₀ may make labor unknown to the mother, predisposing to delivery under unfavorable conditions. Weekly examinations after 32 weeks of gestation are advised; any effacement before term indicates bedrest. Autonomic hyper-reflexia is a major threat. It may be triggered by bowel or bladder stimuli as well as labor itself. Induction of labor has also been associated with a high risk of hyper-reflexia and is relatively contraindicated. Spinal and epidural analgesia and anesthesia seem to decrease hyper-reflexive episodes effectively.^{74, 77}

Abnormal Response to Depolarizing Muscle Relaxants

Of great importance to the anesthesiologist is the massive translocation of intracellular potassium from skeletal muscle to the extracellular space following the administration of a depolarizing muscle relaxant, such as succinylcholine. This phenomenon may occur as early as 3 days after injury and is thought to result from the denervation process of overgrowth and spread of cholinergic nicotinic receptors to include extrajunctional sarcolemma. This results in supersensitivity to depolarizing agents, whereby the entire affected muscle mass depolarizes synchronously and releases large amounts of potassium into the circulation.²⁹ A number of important points should be emphasized. First, the magnitude of potassium release is more a function of the amount of muscle mass affected than of the amount of drug given: 20 mg of succinylcholine has been noted to result in a serum potassium concentration of 13.6 mEq per L.⁷² Also, the causative overgrowth of receptors may well occur before spasticity replaces flaccid muscle paralysis. Finally, pretreatment with a "defasciculating" dose of non-depolarizing relaxants does not reliably block the occurrence of significant hyperkalemia. Because the precise onset of supersensitivity is unpredictable, depolarizing agents should be avoided in all SCI patients.

Should the inadvertent administration of succinylcholine occur, ECG changes progress from atrial conduction disturbances to prolonged PR interval (>7 mEq per L), tall peaked T waves (7 to 9 mEq per L), progressive widening and aberration of the QRS complex (>6 to 7 mEq per L), and finally to sinusoidal ventricular complexes and ventricular fibrillation when serum potassium concentration exceeds 12 to 14 mEq per L.

Pharmacologic treatment includes intravenous sodium bicarbonate (44 to 88 mEq) and glucose-insulin (1 to 2 units per 5 g of dextrose) to shift potassium intracellularly, as well as calcium (0.5 to 1 g) to antagonize the membrane effects of potassium. Hyperventilation may also be employed acutely. If circulation fails, CPR is, of course, mandatory to support cellular metabolism, which will re-sequester the potassium in 10 to 15 minutes, as well as to circulate resuscitative drugs.

Altered Thermoregulation

Temperature regulation is impaired for a number of reasons. Afferent information to the hypothalamic thermoregulatory center is interrupted. Sympathetic denervation causes cutaneous vasodilation that increases heat loss. Also, inability to shiver limits the ability to increase body temperature. Spinal cord injured patients, therefore, become relatively poikilothermic. Efforts to avoid both hypothermia and hyperthermia are necessary. The use of a heating-cooling mattress, variable operating room temperatures, the adjustment of ventilator circuit temperature and humidity, and intravenous fluid temperatures tailored to the situation will allow either raising or lowering body temperature as indicated.

Other Systemic Alterations

SCI produces alterations in a number of other systems, the more salient of which will be summarized here. Several recent reviews detail and discuss these and other sequelae in more detail.^{53, 71} Besides the changes in fluid and electrolyte status caused by the occurrence of renal insufficiency, hypercalcemia and hypercalciuria have been observed in the early stages of SCI. This phenomenon occurs most often in young male patients, seems to result from calcium release from denervated (flaccid) muscle and possibly from bone stores, and occurs in the first year with a peak around 10 weeks postinjury. It is more common in higher level injuries; serum sodium and parathyroid hormone levels are usually normal.¹⁰ When hypercalcemia is severe, hypertension and ventricular arrhythmias may occur. Treatment includes hydration with saline, potent diuretics, glucocorticoids, and, if necessary, calcitonin. In contrast, long-term SCI patients develop osteoporosis, which results from increased calcium loss. In the case of supervening renal failure, these individuals may develop hypocalcemia and pathologic fractures.

Average metabolic rates are usually depressed after injury but catabolism and hypoproteinemia can occur acutely especially when infection occurs. Increased protein and caloric intake can overcome this tendency.

When assessed, endocrine function usually remains normal except for two possible exceptions. A number of investigators have documented moderate glucose intolerance, often with hyperinsulinemia, suggesting relative resistance to endogenous insulin (glucagon levels are normal).¹⁷ Secondly, the potential for adrenal insufficiency after steroid therapy warrants consideration.

In patients with normal kidney function, hematologic studies show anemia in 52 per cent of cases and demonstrate either the normocytic, hypochromic (56 per cent) or normochromic (32 per cent) types. Possible causes for these anemias include increased plasma water in response to augmented venous capacity, significant decubiti, as well as chronic or severe urinary tract infections.

The digestive system is affected as well. Acute gastrointestinal bleeding occurs in up to 20 per cent of patients. Gastric distention, ileus, and nonspecific liver dysfunction (with a normal serum bilirubin) are common complications, usually occurring during the first week postinjury and resolving over several weeks, although occasionally persisting longer. Pancreatitis also occurs, but its relationship to cord injury per se is unknown. Diagnosis of these and other intra-abdominal emergencies may be difficult because of altered sensation. Vomiting may occur *without* pain or nausea. The newly described syndrome of gastroduodenal motor dysfunction, possibly secondary to loss of adrenergic inhibitory control, features altered motility, pain, and vomiting. It is seen in certain SCI cases and responds to low doses of adrenergic agonists such as ephedrine.⁷⁰ Gastric and bowel distention and the tendency toward vomiting in most of these disorders warrants a high index of suspicion and preparation for airway protection on the part of the anesthesiologist. The distention itself may embarrass ventilatory ability.

Last but not least, chronic pain is a problem in many of these patients. It can cause and reinforce the tendency toward depression that is often present. Proper management of pain and psychosocial support have proven essential for adaptation and rehabilitation of the patient.

ANESTHETIC MANAGEMENT

In view of the high percentage of SCI patients with associated injuries, the anesthesiologist may be required to care for these patients during initial diagnostic procedures, during emergency operations aimed at managing life-threatening trauma elsewhere in the body (for example, closed head injury, hemorrhage), for emergency spinal decompression, or for other procedures (for example, urologic, plastic surgeries) during the more chronic phase of injury. The foregoing discussion of acute and chronic derangements in systemic function provides the basis for rational and safe anesthetic management as well as daily care of these patients.

In acutely injured patients, maintenance of normal acid-base and blood-gas parameters, as well as adequate spinal cord perfusion pressures assumes paramount importance. Experimental work in cats suggests that neither hypercarbia nor hypocarbia confers therapeutic advantage over normocarbia in terms of both neurologic recovery and histologic tissue preservation. Although not statistically significant, a study²⁵ of mortality and tissue preservation indicates that hypocarbia may be less harmful than hypercarbia in the acute postinjury period. Consequently, it seems prudent to maintain PaCO_2 in the 35 to 40 mm Hg range. Management of closed head injury with increased intracranial pressure would take precedence in this area.

Hypoxemia must be prevented by careful attention to management of significant physiologic shunting, which occurs when PaO_2

values are less than 60 mm Hg with an FIO_2 of 50 per cent. Possible contributing etiologies such as hemothorax or pneumothorax, pulmonary embolization of fat or thrombi, foreign body or gastric content aspiration, and noncardiogenic pulmonary edema should be searched for and either excluded or treated appropriately. PEEP may be required to decrease shunting and increase oxygenation once pneumothorax or other reversible causes of hypoxemia have been excluded. However, the possible negative effect of PEEP on cardiac output and intracranial pressure must be considered. In case the patient is not already intubated and this is necessary, it should be carried out as described previously.

Cardiovascular management, as discussed already, most frequently requires judicious repletion of intravascular volume to restore normal venous return and filling pressures. During the phase of spinal shock, lasting anywhere from 3 days to 6 weeks (average of 3 weeks), the advantages of pulmonary artery catheter monitoring are obvious in maintaining hemodynamics and avoiding pulmonary edema. Potent inhalation agents may cause a significant dose-dependent myocardial depression in acutely quadriplegic patients. Judicious volume loading, avoidance of myocardial depressant drugs, and low-dose dopamine in situations of decreased tissue perfusion should precede the use of peripheral vasoconstrictors, such as phenylephrine, to preserve the favorable cardiac effects of decreased afterload. Optimum cardiac function in quadriplegic patients has been reported to occur at pulmonary capillary wedge pressures at or below 18 mm Hg.⁵⁴

The electrolyte, neuromuscular, and other potential systemic alterations should be noted, with management of the procedures as outlined previously. As noted by Schonwald et al,⁶⁶ both a sufficiently deep general anesthetic technique, employing halothane or enflurane, and regional anesthesia (subarachnoid or epidural) effectively prevent episodes of autonomic hyper-reflexia. An alternative, where surgical considerations requires high spinal levels (above T_5), is a subarachnoid block followed by light general anesthesia with endotracheal intubation and controlled ventilation. A study⁴² in dogs demonstrated statistically significant increases in lumbosacral SCBF with a lesser, nonsignificant tendency toward increases in thoracic and cervical cord flow after subarachnoid injection of tetracaine, as long as mean arterial pressure remained above 100 mm Hg. This favorable effect was blocked by the addition of epinephrine to the tetracaine; in fact, a nonsignificant tendency toward decreased thoracic and cervical cord flows actually occurred. Hence, spinal anesthesia may improve cord blood flow, but vasoconstrictors should not be added to the anesthetic. Continuous intra-arterial and pulmonary artery pressure monitoring enhances safe management of any of these techniques as well as the detection and management of hyper-reflexic breakthroughs.

Nitrous oxide/oxygen/narcotic-based techniques (balanced anesthesia) seem less recommendable in light of their failure to prevent hyper-reflexia in 2 of 9 patients. Regardless of the technique employed, direct acting arteriolar dilators (for example, nitroprusside),

alpha-adrenergic blockers (for example, phentolamine), antiarrhythmics (for example, lidocaine, propranolol), and atropine should be readily available.⁷⁰ The need to avoid succinylcholine is reiterated; however, the new, short-acting nondepolarizing agents make this constraint clinically tolerable because they are a reasonable alternative.

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tion, decompression, or excision of vertebral bodies in fractures of the thoracic and lumbar spine with displacement or neurologic compromise; and lastly, the treatment of severe spinal deformities, such as scoliosis, kyphosis, and lordosis.⁹ Depending on the indications for operation and the location of disease, a thoracic or a thoracolumbar approach to the spine will be used for thoracic or lumbar procedures, respectively. Although any operation on the spine carries a considerable risk, the technical perturbations, at least from an anesthetic perspective, are less complex in lumbar operations. In this circumstance, the spine is approached by excision of the 11th or 12th rib, detachment of the diaphragm at its periphery, and movement of the peritoneum anteriorly for retroperitoneal approach to the lumbar area. Although not inconsequential, the thoracolumbar method obviates the need for endobronchial intubation, one-lung ventilation, and the complexities associated with thoracotomy. The remainder of this article discusses issues primarily associated with, but not exclusively limited to, transthoracic spinal surgery.

With this approach, the surgeon pursues the spine through a lateral thoracotomy (Fig. 1). In the absence of an associated scoliosis, a left thoracotomy is favored, for the aorta is more easily mobilized and repaired than the vena cava in the unlikely event of vascular injury. As a rule of thumb, the convexity of the scoliotic curve is approached because the great vessels will customarily be displaced into the concavity of the curve.² The thoracic incision is usually placed over the rib that leads to the apex of the curve, if a free rib graft is planned.²² A subperiosteal resection of the rib is carried out, and the rib is retained for later use in grafting. The surgeon then incises the mediastinal pleura vertically, elevating flaps from the vertebral column. Segmental vessels are readily identified over the body of vertebrae and are ligated proximally and distally, a substantial distance away from the intervertebral foramina, so that the risk of vascular insult to the spinal cord is minimized. Following mobilization and, if necessary, division of the anterior longitudinal ligament, the corrective surgical procedure is carried out by (1) removal of the intervertebral disks, (2) excision of the affected vertebral bodies, (3) spinal cord decompression, when necessary, and (4) curettage of slots in both the upper and lower vertebral fusion limits for acceptance of the strut (rib or fibula) graft. Through pressure exerted on the apex of the spinal curve by an assistant, and concomitant distraction by the anesthesiologist, the fibular or rib strut grafts may be measured and so fitted into their appropriate slots. With added stability as the goal, the surgeon often uses more than one graft, because those placed more than 4 cm from the apex of the kyphotic curve have a higher chance of fracture. Once traction is discontinued, the grafts will be locked in place. Following removal of periosteum, the bleeding bone surfaces of the anterior aspects of the vertebral bodies facing the strut grafts are curetted to remove all soft-tissue debris, and the space is filled with chips of rib or iliac bone. The intervertebral spaces are also filled with bone graft. Following stabilization of the spine, the pleural flaps are closed, and

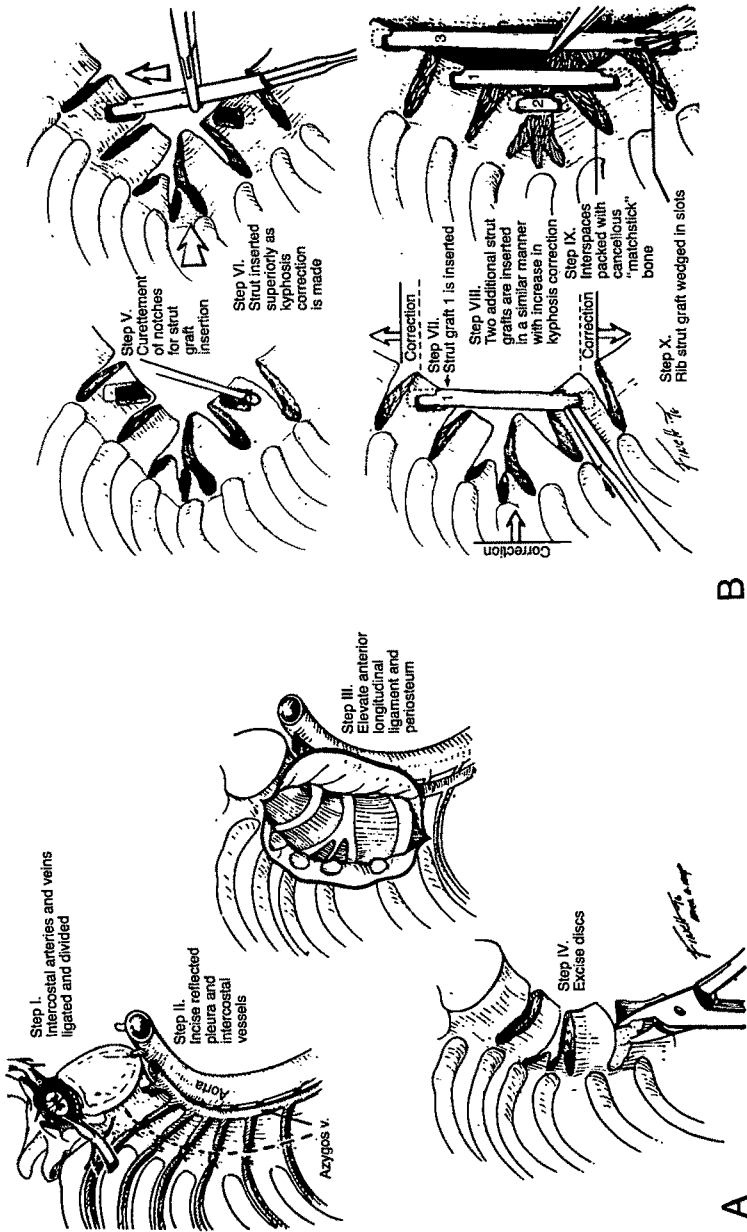


Figure 1. (A and B) Strut graft technique. (From Bradford DS, Winter RB, Lonstein JE, et al: Techniques of anterior spinal surgery for the management of kyphosis. Clin Orthop Rel Res 128:129-139, 1977; with permission.)

thoracostomy tube drainage is instituted during repair of the thoracotomy incision.

The procedure may be completed expediently and the spine stabilized promptly through the respective use of one-lung ventilation and vascularized strut grafts. Without doubt, a majority of thoracic surgeons feel that the operation can be more quickly accomplished in the absence of a ventilated lung, because an inflated lung obscures exposure and necessitates retraction. On the other hand, the use of vascularized strut grafts generates greater controversy. The available experimental evidence indicates that both vascular and nonvascularized grafts undergo demineralization, absorption, and replacement over time. In the nonvascularized circumstance, this replacement may take as long as 2 years for completion, with the graft being weakest at 6 months postoperatively. Laboratory data corroborate the similarity of bone repair in both vascular and nonvascular grafts, beginning with resorption and followed by appositional reactive bone formation. However, the time intervals and the sequence are accelerated in the vascularized grafts.²¹ From an anesthetic point of view, important ramifications of this issue include additional surgical time for vascularized grafting, combined with the provision of adequate systemic arterial hydrostatic pressure and suitable rheologic characteristics of blood, both of which enhance blood flow to the graft in the postoperative period.

The anesthesiologist must take special precautions in cases involving spinal cord tumor (for example, plasmacytoma and certain metastatic lesions), acute fractures, and infections, because blood loss in these circumstances can be substantial. Therefore, availability of an adequate volume of autologous as well as homologous blood combined with generous access to the circulation should be included in any preoperative anesthetic plan. Furthermore, most patients undergoing a significant anterior spinal surgery can be expected to have an ileus for several days postoperatively. Although a few patients recover rapidly from this, most require a period of gastrointestinal decompression and withholding of postoperative feedings. In most centers, nasogastric tubes are inserted at the time of operation. When severe physical debilitation, such as that caused by malignancy or trauma, antedates surgery, the preoperative initiation of parenteral nutrition seems appropriate.

ENDOBONCHIAL INTUBATION

Although procedures involving the thoracic spine are not found on the list of highest priorities for endobronchial intubation, most surgeons would agree that the facilitation of exposure provided by one-lung ventilation makes this a most attractive and desirable intervention.¹⁵ For the anesthesiologist, indications should include a surgeon who requests it and patients who can derive important benefits from this surgical enhancement. The availability of many different double-

lumen endobronchial tubes only serves to complicate matters. For simplicity, only right and left plastic disposable Robert Shaw double-lumen endobronchial tubes will be described here. This naturally leads to the questions: (1) why disposable tubes, and (2) what is the basis for choice between right- and left-sided tubes?

Disposable tubes have the following characteristics: a brilliant blue endobronchial cuff, which one easily visualizes during bronchoscopy; high-volume, low-pressure cuffs that minimize pressure-induced tracheal injury; a right endobronchial cuff that allows ventilation of the right upper lobe through a ventilation slot; packaging with a removal stylet and nonadhering suction catheters; and construction with clear plastic, which permits not only the observation of tidal movement of respiratory gas, moisture, and secretions but also endobronchial blood. These features, not found in traditional endobronchial tubes, certainly recommend the use of disposable tubes.

With these advantages in mind, should it matter which bronchus is intubated? The answer is definitely yes, for reasons recently clarified by Benumof and his colleagues.¹ Through their efforts, clinicians now have clear-cut guidelines based on a good scientific foundation. These investigators have defined the margin of safety (for placement of a double-lumen tube) as the length of the tracheobronchial tree within which an endobronchial tube may be moved or positioned without obstructing a conducting airway. In doing so, they measured the length of right and left mainstem bronchi both *in vivo* and *in vitro*, using fiberoptic bronchoscopy, dissection of cadavers, and measurement of pre-existing lung casts. Additionally, the length of various double-lumen tube segments and variations in the specifications for all adult-size double-lumen tubes were examined. They defined the most distal acceptable position of a left-sided double-lumen tube as that in which the left endobronchial lumen tip rests at the proximal margin of the left upper lobe bronchus. Additionally, the distance between the right and left lumen tips must exceed the length of the left mainstem bronchus, so that when the tube is in this distal position, the orifice to the right side remains in the trachea. Otherwise, the right mainstem bronchus will become occluded leading to right-sided atelectasis. Examples of this, as well as the following possibilities, are clearly delineated in Figure 2. Thus, the margin of safety in positioning a left-sided double-lumen tube is the difference between the length of the left mainstem bronchus and the length of the tube between the proximal margin of the left endobronchial cuff and the left lumen tip. In their study,¹ this difference ranged from 16 to 19 mm. Utilizing similar criteria, they found the margin of safety in positioning right-sided tubes to be from 1 to 9 mm. Patient height, gender, and tube design (different manufacturers) accounted for variations. The numbers clearly indicate a much larger margin of safety for left-sided endobronchial intubation than for the right. Expectantly, the authors preferred left-sided double-lumen intubation because of the greater margin of safety. However, this does not preclude confirmation of proper position of either left- or right-sided tubes with fiberoptic bron-

plex. On the left side, the margin of safety is smallest when the left mainstem bronchial length is short and the length of the proximal margin of the left cuff to the left lumen tip exceeds the manufacturer's stated specification by 2 mm. When this distance is 32 mm, one can see that the chance for obstruction of the left upper lobe or right mainstem bronchus increases as the length of the left mainstem bronchus decreases below 32 mm. In the study by Benumof and associates,¹ four patients (two males and two females) had left mainstem bronchial lengths equal to or less than 32 mm. Left upper lobe bronchus obstruction was confirmed in one during the operation. On the right side, the smallest safety margin occurs when the right mainstem bronchial length is less than the length of the right endobronchial cuff (10 mm). Benumof and coworkers¹ found an 11 per cent incidence of right mainstem bronchial lengths less than 10 mm.

Right endobronchial intubation in this subgroup produce partial or complete obstruction of the right upper lobe bronchus. This datum clearly demonstrates that left-sided endobronchial double-lumen tubes should be used in all cases involving the thoracic spine. The only circumstance contraindicating the use of a left-sided tube is a surgical procedure directly involving the left mainstem bronchus, for example, a left pneumonectomy.

Once inserted, the position of the double-lumen tube is confirmed using a flexible fiberoptic bronchoscope. Although the bronchoscope can be used to facilitate the actual process of tube insertion, usually this is not necessary. For many years, most clinicians have employed conventional tube clamping and auscultation to document proper tube position. However, the subsequent use of bronchoscopy demonstrates that this traditional method yields a malpositioned tube in up to 48 per cent of cases. Possible double-lumen malpositions, often occurring after auscultation and clamping alone, are presented in Figure 3. After placement of a left-sided endobronchial tube of a size 37 French or larger, a 4.9-mm external diameter pediatric fiberoptic bronchoscope should first be passed down the right (tracheal) lumen. Upon exiting this lumen tip, a clear view of the tracheal carina should be seen straight ahead. The left endobronchial tube should be seen going off to the left, and the upper surface of the blue endobronchial cuff should be seen lying just below the left side of the tracheal carina. Obviously, overinflation of the endobronchial cuff leading to herniation across the carina and obstruction of the tracheal lumen will be detected immediately with the fiberscope. Overinflation of the endobronchial cuff may also produce high cuff pressures, which can cause extrinsic compression of the endobronchial lumen, thereby limiting passage of the scope through the left side of the tube. Normally, once the scope exits the endobronchial limb, flexion of the scope upward should reveal the left upper lobe bronchus, whereas a straight ahead view should reveal the left endobronchial carina. Some circumstances (for example, when an endobronchial lesion exists along the path of the endotracheal tube or conventional, direct laryngoscopy is not possible) preclude the use of a double-lumen endobronchial tube. After

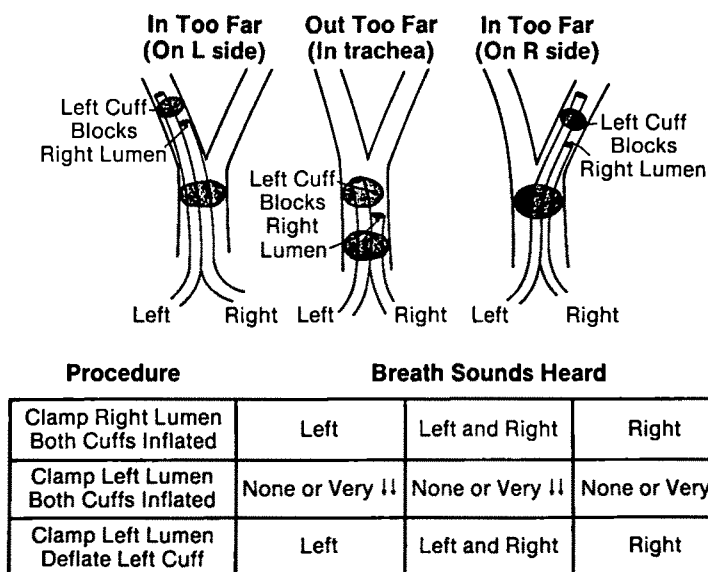


Figure 3. Three major malpositions of a left-sided double-lumen tube and the breath-sound diagnostics accompanying these malpositions. (From Benumof JL: Separation of the two lungs [Double-lumen tube intubation]. In *Anesthesia for Thoracic Surgery*, ed 1. Philadelphia, Saunders, 1987; with permission.)

properly positioning the endobronchial tube and appropriately inflating the cuffs, the anesthesiologist exercises caution while turning the patient to the lateral decubitus position by keeping the patient's head maintained in a neutral position. Any flexion or extension of the patient's head will produce an inward or outward movement of the endobronchial tube, respectively. Once the patient has been secured laterally, some authorities reconfirm tube position with the bronchoscope, since even small changes in tube position brought about by patient movement may exceed the rather small safety margin for endobronchial tubes. Bronchial rupture, as well as other forms of tracheobronchial damage, can occur during positioning. Careful attention to the avoidance of tube movement, as well as to endobronchial cuff deflation prior to positioning, should obviate these complications. Although the use of a tube too large for an individual patient will understandably result in airway trauma, anatomic measurements have delineated that a 37 French or larger tube can be used in almost all adult females and a 39 French tube or larger in almost all adult males.

ONE-LUNG VENTILATION

The presence of a double-lumen endotracheal tube necessarily specifies one-lung ventilation. Before considerations germane to one-

lung ventilation can be entertained, however, the physiologic impact of the lateral position and the open chest must first be discussed.

In a spontaneously breathing and laterally positioned patient, an opened nondependent hemithorax induces mediastinal shift and paradoxical respiration, both of which will negatively affect gas exchange. Owing to gravitational effects, the dependent hemithorax has less negative intrapleural pressure and undergoes a reduction in size due to compression by the overlying mediastinum. Both events act to decrease the volume of dependent lung. Furthermore, the loss of negative intrapleural pressure occurring in the opened upper chest generates further gravitational effects on the mediastinum, promulgating additional movement toward the dependent hemithorax. Spontaneous ventilation, especially the inspiratory phase, accentuates this downward mediastinal shift even more. Also, because of the lateral position, the abdominal contents cause greater cephalad movement of the dependent diaphragm during exhalation, with the majority of the pressure exerted on the lower or anatomically posterior part of the diaphragm. In this circumstance, caudal diaphragmatic excursion most effectively and efficiently expands the dependent lung. Spontaneous ventilation, although not recommended, brings about more efficient expansion and ventilation of the dependent lung,²⁵ which, at the same time, also has the greatest perfusion.

The regional differences in ventilation and perfusion of the lung in upright man have been well described. The assumption of the lateral decubitus position causes several perturbations. In upright man, the right lung receives roughly 55 per cent of total lung blood flow, whereas the left receives the other 45 per cent.²⁵ In the lateral position, the nondependent lung always receives proportionally less perfusion, regardless of its overall anatomic size. When the right hemithorax is nondependent, it receives approximately 45 per cent of total lung blood flow. In comparison, the left lung receives 35 per cent when nondependent. Obviously, the dependent lung always receives proportionally larger blood flow due to gravity. This increased blood flow is matched by increased ventilation when the patient breathes spontaneously, for reasons cited previously.²⁵ However, it should not be assumed that these statements in any way recommend spontaneous ventilation during this operation.

Anesthesia, per se, does not alter lung perfusion, but it does affect ventilation by causing proportionally greater ventilation of the nondependent lung. This occurs because of the well-known influences of anesthesia on functional residual capacity (FRC), thereby lowering the FRC of the dependent lung, pushing it to a lower and flatter part of the pressure-volume curve, and resulting in a relatively noncompliant situation. Muscle relaxation also predisposes to altered ventilation patterns. During anesthesia, an increased FIO_2 and poor secretion clearance may compound this negative effect on FRC of the dependent lung. Cephalad displacement of the dependent diaphragm and the downward shift of mediastinal weight also impair ventilation. Application of positive end-expiratory pressure (PEEP) to both lungs,

or PEEP to the dependent lung and zero end expiratory pressure (ZEEP) to the nondependent lung, improves ventilation and compliance of the dependent lung. Alternatively, some clinicians use larger tidal volumes to promote gas exchange. However, the hyperventilated upper lung obscures the surgical field. Higher airway pressures in the lower lung can actually deter gas exchange by diverting blood flow from the dependent lung to the nondependent lung. Surgical retraction and lung compression, albeit not physiological, act to beneficially affect ventilation-perfusion relationships by diverting blood flow back to the dependent ventilated lung. In summary, the anesthetized and paralyzed patient in the lateral position with an open chest has a relatively noncompliant and overperfused dependent lung, with additional lung volume losses possibly being induced by cephalad movement of the diaphragm, a higher FIO_2 , and poor secretion clearance.

To complicate matters, the surgeon says, "Please deflate the nondependent lung," and the pathophysiologic evolution continues. From the previous description, it is clear that a shunt compartment has been created in the dependent lung, resulting in an increased alveolar-to-arterial oxygen tension difference and impaired oxygenation. It should come as no surprise that deflation or the absence of ventilation of the nondependent lung, combined with continued perfusion of that lung will add an obligatory transpulmonary shunt flow to whatever shunt flow may already exist in the dependent lung. This situation may not be as bad as it seems, because several operant mechanisms restrict this shunt flow during one-lung ventilation. Gravitational influences certainly result in less flow to the nondependent lung, whereas surgical compression of lung tissue and kinking of blood vessels during deflation may also decrease blood flow. Coexisting disease in this nondependent lung may also produce a fixed decrease in perfusion.

The most potent mechanism acting to limit transpulmonary shunt during one-lung ventilation is that of hypoxic pulmonary vasoconstriction (HPV), which normally produces a 50 per cent reduction of pulmonary blood flow for a single atelectatic lung. As expected, the influence of HPV permits a higher Pao_2 than would be anticipated. Practically, HPV can raise the Pao_2 from a dangerously low level to one that permits continued lung deflation and completion of the surgical procedure. For example, the transpulmonary shunt during one-lung ventilation is only 20 to 30 per cent in comparison to the 40 to 50 per cent that would occur without HPV. In spite of evidence suggesting that on a sublobar level good collateral ventilation may be the first line of defense against hypoxemia, and HPV second, that maintenance of mechanisms inherent in HPV are of prime importance to the anesthesiologist participating in this procedure.

Experiments demonstrate those factors that optimize HPV. When the nondependent lung becomes atelectatic in the presence of a normal hemodynamic and metabolic state, HPV decreases blood flow to this lung by up to 50 per cent. Therefore, shunt flow is reduced to 20 per cent of total lung flow, instead of remaining at the 40 per cent

level without HPV. During an FIO_2 of 1.0, the 20 per cent shunt produces a PaO_2 of roughly 280 mm Hg. Isoflurane and other volatile anesthetics inhibit HPV in a dose-related manner⁵; however, the impact of this effect may not be that great. For example, a 1.0 MAC level of isoflurane inhibits the HPV response in the nondependent lung by 21 per cent, so that the existing transpulmonary shunt would increase from 20 to 24 per cent and the estimated PaO_2 would decrease from 280 to 205 mm Hg at an FIO_2 of 1.0. Smaller and larger concentrations of isoflurane will have expectedly smaller and greater negative influences on oxygenation. A 2.0 MAC level of isoflurane is associated with a large decrease in PaO_2 . From this, it is clear that 1.0 MAC of isoflurane combined with intravenous narcotics, which have little or no effect on HPV, permits an FIO_2 of 1.0 and produces only minimal effect on HPV. This explains the findings in one-lung ventilation studies involving intravenously anesthetized patients: the introduction of 1.0 MAC concentrations of either isoflurane or halothane caused little disruption of arterial oxygenation.²⁰ Therefore, use of modest doses of volatile inhalational anesthetics combined with appropriate narcotic supplementation can result in maintenance of HPV and arterial oxygenation.

Hypoxic pulmonary vasoconstriction can also be affected by several other factors, but a maximal response occurs when the pulmonary artery pressure, Paco_2 , and mixed venous oxygen tension are normal, in the absence of vasoactive drugs. Vasodilators indiscriminately dilate the pulmonary vasculature; therefore, drugs like nitroprusside, nitroglycerin, dobutamine, and several calcium antagonists and beta-2 agonists will inhibit HPV. Hypocapnia resulting from controlled hyperventilation increases airway pressure in the ventilated lung, which diverts blood flow to the nonventilated lung. Hypercapnia acts as a vasoconstrictor by selectively increasing the ventilated lung pulmonary vascular resistance, also diverting blood flow to the nonventilated lung. Because of the limited smooth muscle in the pulmonary vasculature, both elevated and decreased levels of pulmonary artery pressure have a negative influence on HPV.

Keeping in mind the factors that affect nondependent lung blood flow, the method by which the dependent lung is ventilated is very important. For instance, if the dependent lung is ventilated with either high airway pressures or PEEP, blood flow will be diverted to the nondependent lung. Hyperventilation of the dependent lung also increases blood flow to the nondependent lung. However, ventilation of the dependent lung with tidal volumes that are too small may produce atelectasis and abnormal gas exchange. For these reasons, logical methods of ventilation of the dependent lung are most important. Although an FIO_2 of 1.0 may cause absorption atelectasis and could conceivably result in some measure of chemical oxygen toxicity, these deleterious effects are more than outweighed by the beneficial effects of an FIO_2 of 1.0 on arterial oxygenation during one-lung anesthesia and vasomotor tone in the dependent lung. Although there is some evidence that an FIO_2 of 0.8 or 0.9, with the balance composed of

nitrogen, may be the optimal inspired mixture, these benefits are not outweighed by the potential for technical difficulty in accomplishing this in the clinical arena. Tidal volumes in the range of 8 to 15 ml per kg are well tolerated, and the recommended starting point is 10 ml per kg with the minute ventilation adjusted to achieve a PaCO_2 of 40 mm Hg. Two-lung ventilation should be continued as long as possible, and the adequacy of gas exchange during one-lung ventilation should be documented by means of serial sampling of arterial blood gases.

Even with optimal management of the variables previously described, circumstances may arise in which one-lung ventilation is associated with hypoxemia. Because blood traversing the ventilated alveoli gives off more than a normal amount of CO_2 , the ventilated lung can eliminate enough CO_2 to compensate for the nonventilated lung. Oxygenation is a different problem entirely, with the development of hypoxemia presenting an important challenge to the anesthesiologist. Because of compression of the dependent lung, it is not surprising that application of PEEP to the dependent lung has been conceived as a potential solution. Realistically, the positive effects of PEEP in increasing the FRC and resolving atelectasis are more than outweighed by the diversion of blood flow to the nondependent lung, which potentiates the development of hypoxia. In patients with very diseased lungs and a low PaO_2 preoperatively, the positive effect of PEEP on FRC of the dependent lung may outweigh the negative influence of blood flow diversion. In such cases, therefore, a short trial of PEEP can be used, when the PaO_2 is below 80 mm Hg. Yet, one must understand that the therapeutic margin of safety of applying PEEP to the ventilated lung alone is quite narrow. A far more efficacious approach entails the addition of 5 to 10 cm of water continuous positive airway pressure (CPAP) to the nondependent lung³ combined with dependent lung ventilation with PEEP. To date, this maneuver has effectively increased the PaO_2 , and the modest distension of the nonventilated lung does not appear to have a negative surgical influence. The combination of PEEP to the dependent lung and CPAP to the nondependent lung produces better oxygenation when compared with the use of CPAP alone in the nondependent lung.

In summary, although one-lung ventilation is not absolutely imperative for this surgical procedure, most surgeons prefer it and believe that it enhances the quality while shortening the duration of operation. This form of ventilation can be optimized through (1) the use of a left-sided endobronchial double-lumen tube, (2) the confirmation of appropriate placement using a fiberoptic bronchoscope, (3) thoughtful positioning in the left lateral decubitus position with appropriate chest rolls and padding, (4) maintenance of normal hemodynamics, and (5) ventilation adjusted to both keep the airway pressure as low as possible and maintain alveolar expansion. Drugs that inhibit hypoxic pulmonary vasoconstriction should be avoided, and those anesthetic agents with limited effects on HPV should be employed in the appropriate doses. When significant degrees of hypoxemia transpire during one-lung ventilation, proper tube position and

optimal hemodynamic and ventilatory factors should be assured, followed by application of CPAP to the nondependent lung and PEEP, if necessary, to dependent lung ventilation.

MONITORING

Just as in many other surgical procedures, patients anesthetized for anterior approach to spinal surgery deserve a thoughtful and meaningful approach to physiologic monitoring. Noninvasive methods of monitoring gas exchange, as well as other physiologic signals, have undoubtedly advanced the quality of care and have become more reliable in the last 5 years. Suffice it to say that noninvasive measurements of circulation, gas exchange, core temperature, and neuromuscular transmission are necessary adjuncts. Certain factors specific to anterior spinal surgery lend added importance to some of these signals. For instance, accurate measurement of core temperature is vital during this operation for two reasons. First, exposure of large areas of visceral surface to a cold operating room environment all too often produces deleterious degrees of hypothermia. Appreciation of the core temperature allows for adjustment of ambient temperature and fresh anesthetic gas flows, as well as warming of intravenous fluids to limit this decrease. Second, knowing the temperature at the end of operation permits one to predict the need for antishivering precautions, since shivering may critically increase oxygen consumption in the postoperative period. Accurate quantitative assessment of the neuromuscular junction permits accurate dosage of neuromuscular blocking drugs intraoperatively, thereby facilitating surgical conditions, and also allows for timely antagonism of neuromuscular blockade at the conclusion of the operation. This obviates the possible contribution of neuromuscular weakness to the need for postoperative ventilatory support. Although capnography and pulse oximetry are generally important to the safe conduct of modern anesthesia, these monitors are proportionately less informative in situations involving the considerable pulmonary physiologic changes frequently associated with one-lung ventilation. For example, with many of the aforementioned conditions induced by the lateral position, open chest, and one-lung ventilation, it is not surprising that the development of increased dead space ventilation and larger alveolar to arterial gradients for CO_2 make the end-tidal measurement of carbon dioxide less indicative of the arterial CO_2 tension and less reliable as a guide to ventilatory adequacy. Although pulse oximetry gives second-to-second indications of global perfusion and hemoglobin-oxygen saturation, it in no way diminishes the need for arterial blood gas measurement, especially during one-lung ventilation.

It should be obvious at this juncture that arterial cannulation and the serial measurement of arterial blood gases to ensure appropriate gas exchange during operation and one-lung ventilation are absolutely necessary. Although invasive and not necessarily devoid of compli-

cations, short-term arterial cannulation performed with proper precautions including a sterile technique is a low-risk invasion. Without question, the derived benefits—objective assessment of gas exchange, minute-to-minute arterial blood pressure quantitation, and a portal for blood sampling—far outweigh the modest risk of distal ischemia and vascular thrombosis.

Because anterior spinal operations are never devoid of blood loss, the importance of intravascular volume assessments cannot be underestimated. It could be argued that urine output serves as a guide of intravascular volume. However, the number of perturbations that can affect it, such as intraoperative increases in ADH secretion, hyperglycemia, and technical problems (catheter kinking or obstruction), make this method too unreliable to stand on its own. For these reasons, either central venous or pulmonary arterial catheterization is warranted, depending on the underlying cardiovascular status of the patient. The positive correlation between right and left ventricular preload in the patient with a healthy heart is certainly well known. The difference in compliance of the two ventricles, with the right being far greater than the left, dictate that changes in right ventricular preload will be proportionally less per mm Hg change than those observed in left ventricular preload for the same increase or decrease in ventricular volume. For the most part, on-line measurement of central venous pressure will be adequate; however, in cases associated with pre-existing right ventricular noncompliance (cor pulmonale),²³ valvular heart disease, congestive heart failure, or important myocardial ischemic disease, this author recommends pulmonary arterial catheterization. Because one-lung ventilation is so much a part of this operation, it should be remembered that when the pulmonary artery catheter lies in the vessels of the nondependent, collapsed lung, measured cardiac output and mixed venous oxygen tension will be lower than actual values. Likewise, measurements obtained from a catheter positioned within an artery of the nondependent lung and recorded during the application of PEEP will be more representative of airway pressure rather than left ventricular preload. Catheterization of the dependent lung vasculature will give accurate readings, either with or without PEEP. Additionally, the mediastinal shift induced by the lateral position not only affects gas exchange but can also distort the mediastinal vasculature such that inaccurately elevated right ventricular preload measurements will result. This more likely occurs in larger, more obese patients. It may dictate the need for pulmonary artery catheterization prior to lateral positioning, for it is technically infeasible to approach the central circulation in this position.

Intraoperative measurement of somatosensory evoked potentials (SEP) have become "the standard of care" for procedures involving the spinal column in patients with an intact and functional spinal cord.¹⁰ During anesthesia and the operation, these signals provide information about neurologic function that would otherwise be unavailable, or apparent only in the unanesthetized patient. Some authorities^{7, 13} believe that recording of SEPs is valuable whenever

pathways amenable to SEP monitoring are at risk. Evoked potentials are derived from the summation or averaging of multiple EEG segments that are precisely time locked to repetitive sensory stimulation, which, for purposes of this discussion, involves the stimulation of either the tibial or peroneal nerves. The averaged SEP waveform is displayed as a plot of voltage against time, customarily described in terms of the post-stimulus latencies and peak-to-peak amplitudes (usually microvolts). Systems for recording evoked potentials include several components: (1) nerve stimulator; (2) electrodes for detecting signals generated by the patient; (3) filters and amplifiers to condition the recorded signals; (4) a computer to control stimulation and signal acquisition and to measure latencies and amplitudes of peaks in the averaged waveform; and (5) devices for display and storage of the SEPs. Until recently, SEPs were measured cortically through the placement of electrodes on the scalp. Because of the profound sensitivity of the cortical-evoked potential signal to the effects of even small concentrations of volatile anesthetic agents, this method has been replaced by direct, near-field spinal cord SEP recording techniques (SSEP). Rather than recording SEPs using scalp electrodes, near-field techniques rely on platinum needle electrodes inserted into the interspinous ligaments (ligamentum flavum) caudal and rostral to the surgical site. This technique is attractive for several reasons: (1) a favorable signal-to-noise ratio; (2) the brief refractory period of spinal cord neurons; and (3) the greater sensitivity of spinal cord potentials to spinal cord damage in comparison to the cortical responses. Moreover, near-field SEP recordings retain their integrity and accuracy in the presence of 1.0 MAC levels of volatile anesthetic agents, whereas cortical responses would be obliterated at this level.

The obvious reason for monitoring intraoperative SEPs is the prevention of spinal cord damage. Several factors aside from anesthetic depth, which are under the control of the anesthesiologist, can confound these signals. Hypothermia, hypotension, and hypoxemia represent only a few.⁷ Four changes in the SSEP commonly occur intraoperatively: (1) a loss of rostral SSEP; (2) an increase in latency of the rostral SSEP, accompanied by a decrease in spinal cord conduction velocity; (3) replacement of the rostral SSEP with a positive injury potential; and (4) the simultaneous loss of both caudal and rostral SSEPs. Observed changes in the SSEP, which are not associated with technical problems but persist despite appropriate interventions by both anesthesiologist and surgeon, are always associated with damage to pathways mediating somesthesia. An increase in the latency of rostral SSEP is associated with a developing intraoperative neurophysiologic defect, whereas the replacement of the rostral SSEP with a positive injury potential signals a transient or permanent conduction block. This potential, however, does not necessarily signify a permanent deficit if forces causing it can be reversed. Simultaneous loss of the caudal and rostral SSEP is most often related to problems of technical origin, such as lead displacement.

Intraoperative monitoring of evoked potentials whether by the

anesthesiologist, the surgeon, or a third party, is an essential part of preservation of the neurologic integrity of patients undergoing anterior spinal operations. Physiologic conditions under the direction of the anesthesiologist, such as suitable anesthetic depth and preservation of spinal cord perfusion through the regulation of arterial pressure and ventilation, should be integrated and fine-tuned, so that the utility of this monitor for the detection of neurologic insult is retained. The anesthesiologist must be alert to changes in the SSEP that are not always of surgical origin and may portend to other non-neurologic catastrophies.

Motor-pathway-evoked potentials are presently undergoing study; however, their practicality has been limited by the necessity of applying electrodes directly on the spinal cord. No reliable data exist, regarding the spinal cord's tolerance to direct stimulation or its sensitivity to changes that are reflected by alterations in the intraoperatively recorded SEP.¹³

ANESTHETIC CONSIDERATIONS

Not unexpectedly, patients requiring spinal surgery with the anterior approach may present with a variety of coexisting, complicating medical conditions. The presence of chronic obstructive pulmonary disease, coronary artery disease, systemic arterial hypertension, and other chronic debilitating conditions, such as diabetes mellitus and carcinoma, primarily dictate the anesthetic prescription. Space limitations do not permit a discussion of the anesthetic implications of each, but aside from some of the previously mentioned nuances of this procedure, the anesthetic plan should be motivated by and adjusted for the presence of complicating disorders. For our purposes here, a few selected issues will be discussed.

The arrival of the new neuromuscular blocking drugs of intermediate duration has virtually supplanted the use of paleo-relaxants, such as pancuronium bromide and metocurine. There is no question that these drugs have a glorious track record of safety in the surgical patient; nevertheless, they are not suited for everyone. The absence of side effects has certainly accelerated the use of the newer drugs; however, they suffer from the potential drawbacks (or advantages, dependent on your perspective) of both a short duration of action and a lack of cumulation, necessitating repeat dosing with relatively large incremental doses. To compound matters, the expense of these drugs is not inconsequential, and this operation is usually not a short one. For these reasons, when drugs such as atracurium or vecuronium are chosen for neuromuscular blockade, and this procedure most certainly necessitates adequate paralysis, administration of these drugs by infusion is warranted. Experimental evidence suggests that a continuous infusion has the benefits of a stable level of neuromuscular blockade, ease of administration, requirement for less drug per unit of time, and predictable antagonism.¹⁸ Additionally, once the appropriate infusion

rate is found, lack of cumulation allows a stable infusion rate for the duration of the case in the absence of intervening factors, such as swings in anesthetic depth or massive blood replacement.

This operation is neither short nor bloodless. In most circumstances, the need for blood transfusion will arise at some time during operation. In today's atmosphere of fear and anxiety concerning the transmission of deadly diseases, such as AIDS and hepatitis, anesthesiologists are increasingly sensitive to these fears, whether perceived or real. When, therefore, is it appropriate to initiate transfusion in patients undergoing this kind of an operation? The physiologic basis for oxygen delivery, the ability for an individual patient to compensate for anemia, and the metabolic burden and benefits associated with transfusion should provide the basis for the proper initiation of therapy in each individual circumstance.

The concept that oxygen delivery is dependent on both the oxygen content of arterial blood and cardiac output is well known. Under normal conditions, oxygen availability exceeds physiologic oxygen consumption by a factor of 4. Oxygen is loosely and reversibly bound to the hemoglobin molecule, as indicated by a low P_{50} . The presence of anemia, per se, is not life-threatening because of important compensatory responses, which include lowered viscosity and improved flow characteristics that serve to maintain oxygen delivery. This principle forms the basis for perioperative hemodilution techniques favored by some.¹² Tissue blood flow and oxygen transport are also preserved during normovolemic anemia by increased myocardial contractility and cardiac output, decreased systemic vascular resistance, and increased oxygen extraction, frequently culminating in lowered mixed venous oxygen tensions.¹⁶ The differential diagnosis of a decreased mixed venous oxygen tension includes arterial desaturation, impairment of cardiac output, decreased P_{50} , decreased red blood cell mass, and increased global oxygen consumption. The overall stability of the patient and the ability for compensation by other systems, with the latter evaluated in part by the level of mixed venous oxygen tension, should collectively serve as the appropriate transfusion trigger, rather than the preconceived notion of adequate hematocrit.⁶ A mixed venous oxygen tension of 25 mm Hg is thought to represent a critical value in designating maximum compensation.

The response of the myocardial circulation to a stressful situation, such as hemorrhagic shock, anemia, globally increased oxygen demand, or altered oxygen hemoglobin affinity, deserves special mention. The human heart functions physiologically near the lower limit of coronary sinus oxygen tensions, so it relies heavily on factors that increase myocardial oxygen supply (that is, coronary vasodilatation) during times of stress.⁸ Compensatory extraction mechanisms are virtually nonexistent. Circumstances such as severe coronary artery disease, in which the coronary circulation is unable to dilate and increase myocardial blood flow, demand the provision of other factors, such as increased hemoglobin concentration and decreased hemoglobin ox-

xygen affinity in order to prevent a myocardial oxygen supply-demand imbalance.

Thus, the appropriate key triggering transfusion necessitates the understanding of oxygen transport. The adequacy of oxygen transport, as indicated by the mixed venous oxygen tension and the patient's compensatory reserves, should also be evaluated. It should be remembered that the most commonly employed transfusion trigger, namely, the hemoglobin concentration, is only one of many factors that should be included in the algorithm leading to blood transfusions. Because of the hazards associated with blood transfusion, it is not inconceivable that the physician may be one day ultimately held responsible for pulling the wrong trigger.¹⁷

Following completion of the operation, but before antagonism of neuromuscular blocking drugs, the double-lumen endobronchial tube should be replaced by a standard single-lumen endotracheal tube using either the oral or nasal route. Certainly, the presence of other unsettling or unstable factors dictating prolonged postoperative supportive ventilation would suggest a preference for the nasotracheal route. At the same time, the position of the nasogastric tube should be assessed, especially if postoperative ventilatory therapy is necessary. Following the assurance of adequate thoracostomy tube drainage and re-expansion of the lungs with PEEP, the patient may be either transferred to the recovery room or intensive care unit for postoperative care, or turned to the prone position for a second-stage, posterior instrumentation and fusion. The absence of randomized definitive clinical studies of two separate operations versus completion of both stages at one time prompts an intuitive clinical decision not necessarily having a factual or scientific basis. It has been our impression that separation of the two stages necessitates the recovery from two operations, rather than from one. Furthermore, posterior fixation and instrumentation serves to partially stabilize the anterior fusion immediately. When patients fare well during the first stage of the procedure with a relatively uncomplicated anesthetic-surgical course, we favor immediate posterior stabilization, regardless of the patient's preoperative medical condition. In patients with more complex medical disorders and debilitation, immediate second-stage operation is favored even more strongly.

POSTOPERATIVE CARE

Regardless of whether one or both procedures is completed on a given day, ventilatory support, at least in the early postoperative period, is indicated. The variability of clinical presentations and the heterogeneity of coexisting diseases preclude the development of absolute management protocols. Certainly, patients with pre-existing pulmonary hypertension, which occurs secondary to their restrictive lung defect and often produces right atrial dilatation and right ventricular hypertrophy, require most careful postoperative ventilatory

support, thoughtful and deliberate weaning, and appropriate metabolic and circulatory attention. At best, these patients manifest contracted lung volumes, reduce chest wall compliance, ventilation/blood flow maldistribution, and increased pulmonary vascular resistance. A preoperative reduction in arterial oxygen tension with a normal PaCO_2 , an increased alveolar-arterial oxygen difference, and an increased dead space to tidal volume ratio are common findings.¹⁴ Frequently superimposed on this are age-related deteriorations in gas exchange,¹¹ thought to be the result of degeneration of the mechanical properties of the lungs, as well as other respiratory functional abnormalities having a selective association (loss of muscle function due to lesions of motor neurons and abnormalities in the central respiratory control system).

Following transfer to either the postanesthetic recovery area or the intensive care unit, these patients are supportively ventilated using tidal volumes and respiratory rates dictated by size, age, and arterial blood gas determinations. We uniformly employ low-dose PEEP because of the well-known effects of position and anesthesia on lung volumes. With few exceptions, patients are weaned using intermittent mandatory ventilation and a progressive decrease of intermittent mandatory ventilation frequency, as determined by arterial blood gas values. Larger and more complicated ventilation-perfusion abnormalities may indicate higher levels of PEEP, but this occurs rarely. The return of normothermia, a stable and responsive circulation, the restoration of intravascular normovolemia, correction of anemia, and the maintenance of physiologic gas exchange on CPAP dictates extubation. In patients with pre-existing lung pathology, standard spirometry values for extubation are uninterpretable in the absence of preoperative spirometry. Therefore, the presence of adequate volumes and capacities does not preclude the physiologic test of ventilatory adequacy indicated by a 1-hour trial of CPAP. The presence of advanced age, intercurrent disease, and neuromuscular abnormalities, like paraplegia or neurofibromatosis, may indicate the need for supportive ventilation for several days, whereas in the least complicated circumstance, the weaning process should take little more than a couple of hours.

Adequate analgesia and the return of adequate ventilatory function following thoracotomy go hand-in-hand. Although fashionable and certainly efficacious, technical circumstances preclude the use of epidural narcotics in these cases. Prior to closure of the chest, intraoperative intercostal nerve blocks two segments above and below the incised dermatome will serve to smooth out the early postoperative period. However, their effect will be limited to less than a day's duration, and may serve to potentially complicate matters, if the blocks are performed too proximal to the spinal cord. Thus, the clinician is left with parenteral narcotics as the foundation of analgesic efforts. In most cases, traditional administration of narcotics, given intravenously or intramuscularly every 3 to 4 hours, is less than effective.²⁴ Appropriate intravenous loading in the early postoperative period using

the patient's discomfort as well as circulatory and ventilatory functions as a guide, followed by patient-controlled analgesia, provides the most effective prescription for pain, short of epidural narcotics.²⁶ The acute postoperative pain team approach has many benefits, and these patients may certainly profit from this.¹⁹

SUMMARY

Although anterior spinal surgery is not new, the frequency with which it is now performed, even in community hospitals, certainly is. The diversity of presentation and the complexities of the physiologic changes demand both a thoughtful and skillful approach to these patients. Underlying physiologic compromise can transform management into a herculean task. The goal of this article has been to provide a foundation for this approach, despite the heterogeneity of these patients, as a group. As with any structure, the foundation is rarely seen, but provides the base upon which we can build.

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Replantation of Extremities

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Replantation refers to the anastomosis of a completely severed part near to its original location. Defined in this manner, the term specifically excludes partially amputated extremities. Establishing this clear dividing line permits accurate comparison of results.

Many centers around the world have established replantation teams. Substantial resource requirements dictate this approach. The longer duration of replantation procedures requires the availability of skilled relief personnel. Regional centers offer optimum and economic use of resources because of greater frequency of the provision of services. The usual personnel required are a surgeon, an anesthesiologist, a scrub technician, and a circulating nurse. The major areas of responsibility in the care of the patient are divided between the physicians. The surgeon concentrates his or her efforts on the wound and replant, whereas the anesthesiologist's attention is devoted to pain relief and the optimization of the patient's physiology for the success of the replant.

Carrell and Guthrie^{3, 4} first reported on limb replantation in 1906. Since these initial descriptions, refinement in instruments, improved suture material, and increased attention to physiology have led to dramatically improved results. Various survival rates of replanted parts have been reported. For example, survival rates range from 46 to 71 per cent for fingers.^{23, 31} Tamai reported an 86 per cent success rate in replants.³⁸ Clear definition of the injury, indications for surgical intervention, and the techniques utilized have resulted in an improved outcome. These advances have made dramatic injuries like those in Figure 1 repairable.

Better understanding of the physiology of blood flow and improved methods to increase flow have also facilitated replant survival. Anesthetic techniques play a major role in this arena. Elimination of many of the body's stress responses and the resultant negative effects of these responses on blood flow is a major beneficial effect of regional anesthesia.

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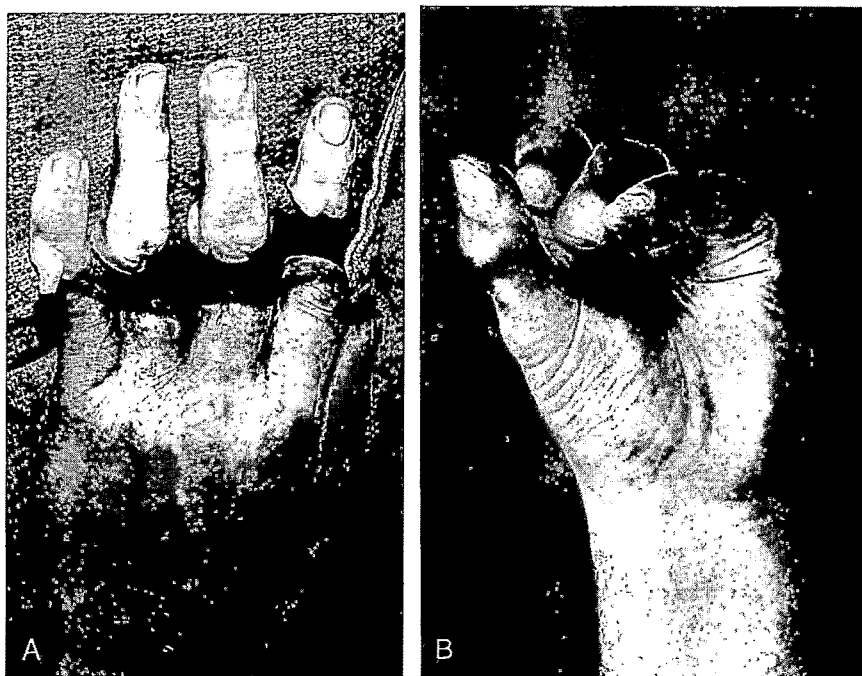


Figure 1. (A) Injury and (B) 1-year follow-up. Used with permission from Louisville Hand Surgery.

PAIN PHYSIOLOGY

The body's reaction to an injury follows a pattern. The initial event is nociception, which is rapidly followed by the perception of pain. A psychological reaction to pain and the injury magnifies the purely physiologic response. The traumatic nature of most amputations imparts a large psychological component to the pain experienced by the patient. This psychological response greatly accentuates the body's release of vasoactive substances. The reduction in blood flow caused by these vasoconstrictors initially attenuates hemorrhage, but later impairs survival of the replanted part.

Information about an injury is transmitted to the brain, primarily by means of two types of nerves, the A-delta and the C-fibers. The A-delta fibers are larger, myelinated, and faster conducting neurons, which convey acute pain of a well-localized nature. In comparison, the unmyelinated C-fibers conduct pain signals more slowly and are responsible for the poorly localized, persistent, and dull components of pain. Locally, the neural signals are reinforced and magnified by chemical products termed algogenic substances.⁵ Serotonin, histamine, and bradykinin are the most common such chemicals found at the site of injury. A dual effect of these substances occurs, enhance-

ment of pain and alteration in local blood flow. The reduction in blood flow produces local acidosis and, as a consequence, the release of vasoactive amines, which, in turn, lead to a greater reduction in blood flow.

Reflex activity also plays a role in the physiologic response to pain. For example, neuromuscular reflexes produce muscle spasm in the injured extremity. Muscle spasm can decrease perfusion at the site of injury while increasing oxygen consumption and acidosis in the traumatized limb. Sympathetic reflexes stimulate sympathetic activity that alters the microvasculature. The negative effects of this reflex activity in the extremity may eventually lead to sympathetic dystrophy. In the more acute replantation setting, this increased sympathetic tone definitely compromises replant survival.

As stated previously, psychological responses add to the physiologic response to trauma. Recognition of a disfiguring injury results in increased catecholamine release, vasoconstriction, and diminished perfusion of the injured part. Stress also causes increased blood viscosity, platelet aggregation, and resultant clotting in the microvasculature.¹ General anesthesia or the use of intravenous sedatives interrupts the psychological component of pain.

Regional anesthesia, by interrupting the pain pathway, eliminates many more components of the pain complex. Complete interruption of the neural pathways removes the reflex sympathetic and motor responses, as well as much of the initiating stimulus of the stress response. Beneficial effects on blood flow and subsequent washout of vasoactive chemicals constitute an additional advantage of regional anesthesia. Vasospasm in the proximal part of the amputation site is subject to both neuronal and hormonal influences. The severed part is affected only by humeral factors. Restoration of blood flow and cooling represent key ingredients in the elimination of the negative factors in the amputated part.

HEMODYNAMIC CONSIDERATIONS

The amputated part will not survive unless the replantation re-establishes perfusion within a relatively short period of time. Successful anastomosis of severed blood vessels is the initial step in the process. Following that, blood flow will be controlled by perfusion pressure, blood viscosity, and the physical characteristics of the vessel.²⁶ Blood pressure directly influences flow, and an adequate pressure maintains the diameter of the vessels in accordance with Laplace's law.

Changes in sympathetic nervous system activity and blood pressure may produce dramatic changes in blood flow. Figure 2 demonstrates the relationship between mean arterial pressure and blood flow through a vessel. Sympathetic stimulation produces a rightward shift of the curve, producing a lower flow at any given pressure. This effect of sympathetic tone results in vasoconstriction or, more specifically,

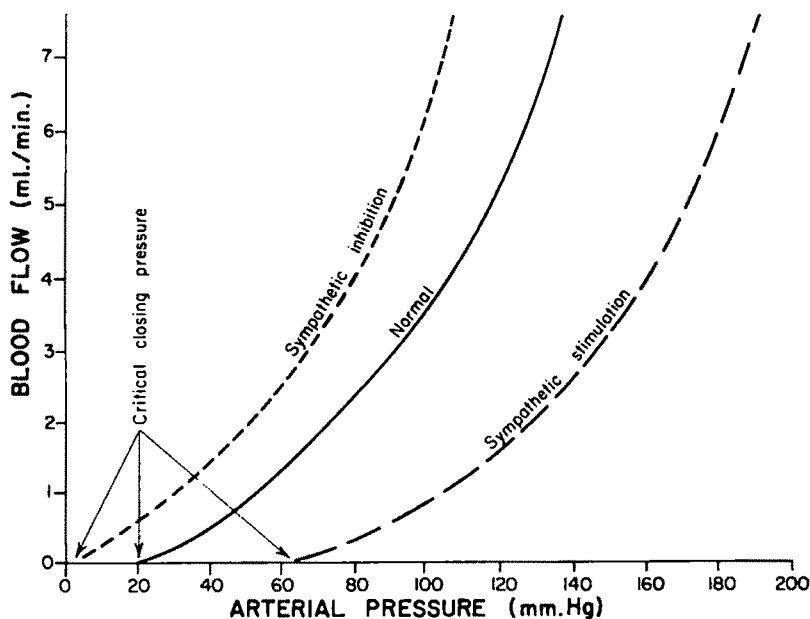


Figure 2. Effect of blood pressure and sympathetic tone on flow. (From Guyton AC: Basic Human Physiology: Normal Function and Mechanisms of Disease. Philadelphia, Saunders, 1971; with permission.)

in a decrease in the radius of the vessel. The effects of vessel radius and other important parameters on ideal laminar flow are described by the Poiseuille equation:

$$F = \frac{(P_1 - P_2) \pi r^4}{8 \eta L}$$

$(P_1 - P_2)$ = pressure difference; r = radius; η = viscosity; and L = length of tube.

Although physicians use Poiseuille's law to describe the dynamics of blood flow, several assumptions in this equation are not true in a blood vessel. Viscosity is not linear in blood and increases exponentially with rising hematocrit values, the major rises occurring above hematocrit levels of 35 per cent (Fig. 3). Blood is not a homogeneous fluid, and the effects of "solids" and cells in the fluid impart very special, nonlaminar characteristics that alter flow. Furthermore, as a result of injury and replantation, the vessel's radius will likely be decreased at the site of anastomosis, a further variable from the ideal equation. Damage to the vessel creates a reduced size and irregular surface, both changes resulting in turbulent flow. During turbulence, the relationships between vessel radius, length, blood viscosity, and flow still exist *in vivo*. However, an absolute correlation does not exist and is not accurate: only trends hold (that is, increased length or viscosity or decreased radius will reduce flow).

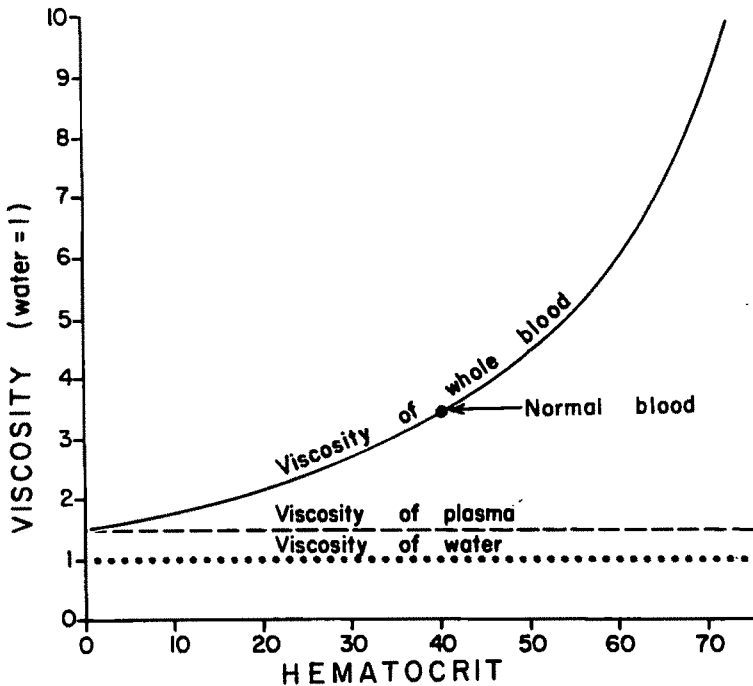


Figure 3. Viscosity changes with hematocrit. (From Guyton AC: Textbook of Medical Physiology, ed 7. Philadelphia, Saunders, 1986; with permission.)

Using this information about flow characteristics, patient care team members can attempt to improve perfusion, primarily by decreasing blood viscosity. Use of low-molecular-weight dextran reduces the rouleaux formation and resultant stasis. Isovolemic hemodilution to a hematocrit of 30 per cent improves viscosity without compromising oxygen delivery significantly^{15, 22, 25} (Fig. 4). The increased blood flow from hemodilution improves survival potential in the amputated part.¹¹ Numerous examples of improved blood flow with lower hematocrit validate isovolemic hemodilution as a therapeutic modality.^{22, 25} Accomplishing hemodilution with dextran 40 and crystalloid avoids some of the edema that occurs after the use of crystalloid alone.²⁶

SURGICAL CONSIDERATIONS

Patient Characteristics

Selection of candidates for replantation is primarily based on surgical considerations. In most cases, an attempt is made to replant am-

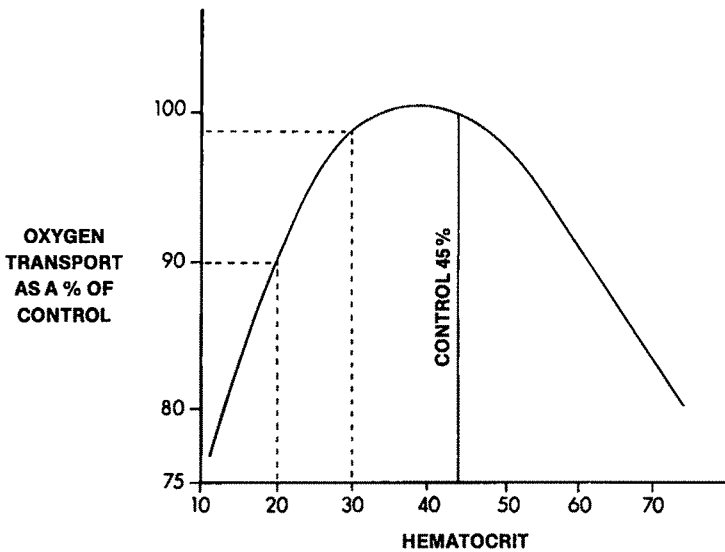


Figure 4. Oxygen transport at various hematocrit levels. (From Shanahan P: *Anesthesiol Rev* Vol X, No. 5, May 1983; with permission.)

puted thumbs. The magnitude and nature of the injury, along with the patient's age, concomitant injuries, and warm ischemia time largely determine whether an attempt will be made to replant other parts.¹³ Lower extremity replantation criteria are more restrictive. Significant internal injuries or life-threatening trauma contraindicates a replant procedure. In addition, warm ischemia time should be less than 6 hours. Minimal crush injury and the absence of gross contamination of the wound are requirements for an attempt at replantation. Several factors occur frequently in this patient population: a full stomach, blood loss (sometime significant), and a prolonged time from injury to arrival at the replant center. As a result, fluid and volume status are of particular importance.

Goldner and associates¹⁴ studied the demographics of replant patients. They found that 85 per cent of their patients were men between the ages of 21 and 30. The average age of patients in a large survey by Wang and others⁴² was 28.8 years. Interestingly, they found that the most common etiology of traumatic amputation was neglect of safety measures. One third of their patients had pre-existing psychopathology,⁴² a common finding in accident victims. Most of these injuries occurred during working hours (6:00 AM to 6:00 PM). The time between injury and initiation of repair approximated 6 hours.

Most patients will arrive at the hospital with significant pain ranging from moderate to severe. Therefore, the psychological impact of the injury usually has time to negatively affect the patient's physiological state. At one time or another, approximately 60 per cent of replant victims require psychiatric intervention.³⁵

Lower Extremity Replants

Replantation of severed lower extremities has not received as much attention as that of upper extremities. Technical difficulties and the greater magnitude of the injury required to amputate a lower extremity have made leg replantations far less common.^{19, 21} The same physiologic principles regarding pain and fluid management during arm replants are used for the lower extremity replant. Regional anesthesia is preferred. Spinal, epidural, or femoral sciatic blocks can be used. Continuous epidural anesthesia is the best method if heparin is not used.

Alternative use of amputated tissues, which cannot be replanted, may result in salvage of the injured extremity as opposed to replantation.⁷ Use of salvaged tissues to cover exposed bone is one example. Bilateral leg injury, with one leg being nonreplantable, may result in a salvage procedure to preserve the other leg.

Surgical considerations include the ability of the site of bony union to withstand load bearing and return of satisfactory sensation to the sole of the foot.¹⁹ Amputations above the knee are usually not replantable because of the large volume of damaged muscle, and most experts attempt replantation only of below-the-knee amputations. The following list presents some of the criteria for lower extremity replantation:³⁹ (1) an experienced replant team; (2) a sharp injury-minimal crush; (3) moderate soft-tissue damage; (4) adequate repair of the tibial nerve; (5) bone shortening of less than 8 cm; and (6) cold ischemia time less than 12 hours.

Psychological problems are more often associated with leg replantations than with arm replants.³⁵

Surgical Requirements

Positioning of the patient, although done in a standard way, must allow the surgeon broad access to the extremity and provide a stable operating field. During a replantation, magnification is essential from time to time. Operating loops and the operative microscope give two levels of magnification. Loops are more difficult to use for long periods because the motion of the surgeon is transferred into motion in the field. In contrast, the operative microscope offers a fixed field from which the surgeon may move his head without a motion effect in the field. The latter prevents the ocular fatigue that occurs when using the loops for prolonged periods of time. The motion of the patient needs to be kept to a minimum during the use of loops and absent when the microscope is used. While repairing bone and tendon disruption, minor movements by a conscious patient give the surgeon no difficulty. However, the repair of vessel and nerve transections requires the microscope and a still field. Additionally, using a malleable lead hand to secure the extremity or the severed part in a fixed position helps.

Elaborate microsurgical instrumentation completes the surgeon's equipment needs. During complicated, prolonged replants, radiant

warmers will keep the irrigation fluids warm. This reduces the tendency toward vasospasm and keeps the tissues moist.

Most surgeons use a padded height-adjustable stool without rollers for sitting. They can lean forward, supporting themselves on their forearms, again reducing the fatigue with prolonged procedures.

ANESTHETIC CONSIDERATIONS

Anesthesia for emergency surgery must consider the overall needs of the patient. Concomitant injuries or disease states may make the patient a poor risk for a lengthy replant anesthetic. Associated trauma is common and, if involving viscera, must be dealt with first. The use of anticoagulation with replants may eliminate the patient with visceral injuries because of the increased potential for internal hemorrhage.

Once a patient qualifies as a replant candidate, the presence of intoxicating drugs must be evaluated. These agents have major interactive effects with general anesthesia, fluid imbalances, and the level of cooperation required for regional anesthesia.

The presence of food or acid in the stomach presents a significant risk of aspiration during deep sedation, especially with general anesthesia. Most replant patients have consumed food in the preceding 6 to 8 hours. Some patients are fed in transit by well-meaning relatives or in referring emergency rooms. Therefore, the anesthesia team must obtain an accurate history about oral intake. The patient with a full stomach should receive treatment in the emergency room. A regime of H_2 histamine receptor inhibitor, a nonparticulate containing antacid such as sodium citrate, and an agent to speed stomach emptying like metoclopramide, reduces the risk of acid aspiration^{8, 12, 16} during deep sedation or general anesthesia for these long procedures.¹⁸ We use this therapy regardless of anesthetic initially chosen.

Initial contact with the patient should avoid painful examinations and convey confidence. Reduction of the pain complex and psychological stress is extremely valuable in patient management. However, prior to use of significant sedation and analgesia, the anesthesiologist should discuss risks and benefits of alternative methods and gain the patient's acceptance of the preferred approach. The advantage of regional anesthesia must be explained thoroughly. Most patients comprehend and accept the regional technique after a thorough explanation.

Occasionally, intoxication requires the delay of the surgical procedure by the anesthesiologist until the patient is more cooperative and able to understand an explanation of regional versus general anesthesia. This decision must be carefully made in consultation with the surgeon and is not the norm. Intoxication or deep sedation by a referring physician that contributes to an uncooperative patient may necessitate general anesthesia given either alone or in combination with a regional block. Anesthesiologists in some centers combine the

advantages of a light general oral tracheal anesthetic (amnesia, better control of ventilation and oxygenation, and a quiescent patient) with those of a regional block (excellent analgesia, sympathetic blockade, and vasodilatation) in such cases and especially in children.

Regardless of the method chosen, appropriate lab studies, including hemoglobin/hematocrit, electrolytes, and toxicology screening (providing the patient is intoxicated) are obtained in the emergency room and reviewed prior to the anesthetic induction.

Regional Anesthesia

The anesthesia technique for replantation has been influenced by many of the factors mentioned previously. Regional anesthesia is preferred for replants, although some controversy exists among centers.²⁸ Based on the length of the procedure, arguments against the use of a regional technique are weak because presently available local anesthetics offer 12 to 18 hours of anesthesia, and continuous techniques can last for days.^{27, 30} Utilization of supplemental techniques may be required for tissue harvesting (skin, free flaps, and veins) or to treat tourniquet pain. As mentioned previously, general anesthesia is one of the supplemental techniques employed, as are other regional techniques. Reblock at another level of the same extremity can also extend the time of anesthesia to accommodate lengthy procedures. Brachial plexus block of the upper extremity is the technique most commonly used,^{6, 27, 30} whereas continuous epidural analgesia suffices nicely for leg replants. Advantages of a regional technique include denervation, sympathetic block, and the safety of consciousness.

Axillary Block. Several techniques for axillary brachial plexus block have been described.^{10, 17} Controversy exists about whether one should elicit a paresthesia for the block.^{11, 37} The incidence of nerve injury reported by Selander et al³⁷ was higher in patients who had paresthesias. However, the patients who had nerve injury received mepivacaine with epinephrine, whereas over half of the patients without paresthesia received plain mepivacaine. Thus, epinephrine rather than paresthesia could account for Selander's findings. The issue of paresthesia and nerve injury has not been settled. Other authorities⁴³ believe that eliciting a paresthesia is important for achieving a successful block. Compression of neural structures with a large volume of local anesthetic is an unlikely source of injury, because a study²⁴ of the sheath's elasticity demonstrates only transient elevations in intrasheath pressures after injection.

The use of a technique employing paresthesia and a large volume of anesthetic agent improves the success rate. The axillary sheath is divided by multiple septa, partitioning the structures in an incomplete fashion.³⁴ Seeking multiple paresthesias is common with the axillary block technique.⁴³ In the circumstances of the patient with incomplete compartmentalization, the multiple paresthesias would seem to be unnecessary.

A modification of a perivascular technique described by Winnie,⁴⁴ which uses a paresthesia, has resulted in a high success rate. Suc-

cessful axillary brachial plexus anesthesia necessitates good understanding of brachial plexus and axillary anatomy. The arm of a supine patient is abducted and flexed at 90 degrees from the body. The axillary artery is palpated as high in the axilla as possible. The anesthesiologist seeks a paresthesia by inserting a short-beveled 22-, 23-, or 25-gauge needle just caudad to the pulse. Subsequent paresthesias, if sought, are located above the artery and cephalad or posterior to the artery. Other anesthesiologists use a transarterial approach, injecting approximately half of the local anesthetic behind and the other half in front of the axillary artery.

The volume of local anesthetic deposited in the axillary sheath is important to ensure blockade of the musculocutaneous nerve, which exits the sheath high in the axilla. For replants, the most suitable agent is bupivacaine in a 0.5 per cent solution. A bupivacaine dose below 3 to 4 mg per kg avoids systemic toxicity.⁹ Recommendations that bupivacaine should be used with epinephrine have drawbacks in the setting of a replantation. The usual dose of epinephrine employed with a local anesthetic may reduce systemic toxicity; however, it may also cause arterial spasm.²⁶ Prevention of the microvascular effects of epinephrine is of major importance. In general, therefore, one should eliminate epinephrine in blocks for replantations. The argument that a longer regional anesthetic occurs with epinephrine is valid; however, the belief that a bupivacaine block will last longer with epinephrine is disputed. This author usually injects 50 ml of 0.5 per cent plain bupivacaine to produce a long-lasting sensory and motor blockade of the arm in adults.

Other Brachial Plexus Blocks. Alternative approaches to the brachial plexus are available, such as the supraclavicular and interscalene methods. Several factors may necessitate the use of an alternative block. First, an alternative block is desirable when an axillary block fails or blocks the plexus incompletely. Second, prolonged surgery may exceed the duration of the local anesthetic, and a second block will extend the benefits of regional anesthesia.

In the setting of a partial or receding axillary block, the partially anesthetized large nerves may not generate a protective paresthesia in response to a needle touch. A more cephalad approach to the plexus avoids the unintentional injury of a nonresponsive nerve. Several techniques are used. The interscalene block, as described by Winnie and Collins,⁴⁴ has many advantages. Simplicity of technique and a low incidence of complications make the interscalene approach to the brachial plexus the most preferred technique for reblocking the arm. This block also provides an alternative for the patient, who, because of pain, cannot abduct the arm for the initial axillary block.²⁰

To perform an interscalene brachial plexus block, one first identifies the interscalene groove at the level of the sixth cervical vertebra, which lies at the same level as the cricoid cartilage. After extending a line laterally from the cartilage to the groove, a short-beveled needle is inserted perpendicular to all planes of the skin. This directs the needle in a medial caudad and dorsad direction, reducing the possible

complications of subarachnoid or vertebral artery injection. The needle is advanced until a paresthesia to the arm is elicited. One then injects a volume of epinephrine containing bupivacaine in a dose required to reach the lower roots, which compose the ulnar nerve. The approximate volume is 30 to 40 ml. The vascular effects of epinephrine in the neck have little impact on the arteries of the extremity but greatly slow the rapid intravascular absorption of the agent.

Pneumothorax is an extremely unusual complication of this block. Occasionally, the phrenic or vagus nerve may be affected owing to the deposition of local anesthetic outside the sheath. Therefore, bilateral blocks should not be performed, to avoid possible respiratory compromise from bilateral phrenic nerve blocks.

Two other approaches to the plexus, the supraclavicular and parascapular techniques, have been described and offer unique advantages and complications.^{40, 45} The supraclavicular block allows the use of a low volume of agent and ensures good blockade of the ulnar nerve. The major drawback is a high risk of pneumothorax (6 per cent).²³ The parascapular block also uses lesser volume and more closely places the local anesthetic to the roots that form the ulnar nerve. However, subclavian artery puncture and injury to the lung are also more likely with this approach than with the interscalene block.

One final regional technique, the stellate ganglion block, offers postoperative vasodilatation. Often blood flow in the replanted part will decrease once the axillary block has receded. A sympathetic block can restore the blood flow and avoid a return to the operating room in many cases. The technique used most commonly is to inject a volume of local anesthetic, approximately 10 ml, over Chassaignac's tubercle on the side of the injury.

Epidural Anesthesia. Continuous lumbar epidural anesthesia is the optimal anesthetic technique for lower extremity replants, which, although not lasting as long as multi-finger cases, often exceed the duration of a spinal anesthetic. The continuous epidural technique offers a duration to match the operative time. Additionally, postoperative pain relief and sympathetic blockade improves the patient's comfort and the blood flow to the extremity. As for brachial plexus blocks, we believe that 0.5 per cent bupivacaine is the best local anesthetic for maintenance of continuous epidural anesthesia.

When the surgeon plans to use heparin intravenously during the early phase of surgery, a single-shot epidural, spinal, or femoral sciatic block may be preferred. General anesthesia is the final alternative for lower extremity replantation. In the event that free tissue transfers are necessary, general anesthesia may be used for latissimus dorsi flaps or skin grafts from areas other than the lower extremities.

Local Anesthetics. The long duration of action of bupivacaine, an amide compound, makes it a good choice for replant surgery. The duration may exceed 12 hours and routinely lasts 8 hours in the axilla. An unexplained, prolonged analgesia that occurs after return of sensation is an added benefit of this local anesthetic.²⁹ This residual effect decreases the need for systemic analgesics. The avoidance of narcotics

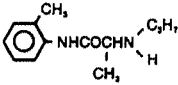
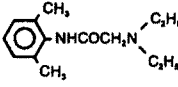
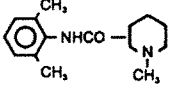
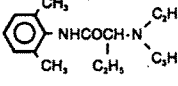
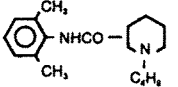
	Formual	Toxicity	Pka	Plasma Protein Bound
Prilocaine		1	7.9	55 %
Lidocaine		2	7.9	60-75 %
Mepivacaine		3	7.6	70-84 %
Etidocaine		4	7.74	94 %
Bupivacaine		5	8.01	88-96 %

Figure 5. Comparative features of commonly used local anesthetic agents. Bupivacaine and etidiocaine are the most lipid-soluble and produce the longest duration of action. (From Mazze RI, Dunbar RW: Anesthesiology 27:574, 1966; with permission.)

postoperatively allows for earlier oral intake. Bupivacaine metabolism occurs in the liver via microsomal enzymes, while the kidneys excrete the metabolites. Bupivacaine is a highly protein-bound compound (88 to 92 per cent). It is also one of the most toxic local anesthetics (Fig. 5). The onset of a block is slower with bupivacaine, sometimes exceeding 20 minutes. Etidocaine also produces a long duration of action and can be employed for replants. One reported drawback with etidocaine is the presence of motor blockade without sensory blockade in some cases.

Prilocaine, lidocaine, and mepivacaine remit too rapidly to be used for these surgeries, unless a continuous regional method is planned.

General Anesthesia

Although regional techniques offer many advantages, general anesthesia remains an important alternative. This author uses both the balanced and inhalational methods for general anesthesia. The lengthy nature of the surgery causes accumulations of the anesthetics in the patient and a prolonged recovery. Heat loss during surgery may cause shivering in the recovery room and is an important consideration with general anesthesia. Heat accumulation in small children, and a few adults, occurs in lengthy replantation. Both temperature changes

need to be addressed. Warming lamps and fluid warmers reduce the possibility of shivering and help reverse the decreased temperature. Increases in temperature under surgical drapes are more difficult to correct, hyperthermia must first be evaluated in reference to the possible pathology, that is, sepsis, malignant hyperpyrexia, blood product reaction, and so forth. Exposure of the patient to the operating room air and use of partial sponge baths often stabilizes the temperature.

Isoflurane offers vasodilatation along with anesthesia. This author uses it in preference to halothane or enflurane. The newer potent narcotics, fentanyl, sufentanil, and alfentanil, form the basis of the balanced anesthetic technique. Fentanyl remains the most popular of the newer agents for prolonged general anesthesia. Nitrous oxide continues as an adjunct to the narcotics in the balanced technique.

All general anesthetics must be administered as if the patient for replantation has a full stomach. A rapid sequence induction using the Sellick maneuver (cricoid compression of the esophagus) affords some safety to prevent aspiration. A nasogastric tube to reduce gastric distension and contents after intubation will decrease recovery room nausea.

OPERATING ROOM MANAGEMENT

Patient comfort extends beyond pain relief to positioning, temperature control, and operating room ambience. These factors are especially important for the patient who is awake and anesthetized with a regional block.

Patient Positioning

Optimal positioning and a thorough padding of the operating table are essential to the success of regional anesthesia in long procedures. The operating table should be padded with an egg-crate foam mattress in addition to the standard pad. Most patients prefer a table positioned with the head slightly up and the knees flexed (chaise lounge position). However, the table is repositioned as needed to provide maximum comfort for each individual. Adequate warm blankets are placed to eliminate patient shivering and subsequent vasoconstriction. Additionally, a warming blanket can be placed on the bed. A Foley catheter needs to be inserted to eliminate the discomfort and commotion associated with a full bladder. The use of a local anesthetic gel and small intravenous narcotic doses minimizes the discomfort during Foley insertion. Standard monitoring of ECG, noninvasive blood pressure values, oximetry, and temperature are employed and do not adversely affect patient comfort. In some centers, the anesthesia team places a radial artery cannula for precise pressure measurements and for blood work, especially when general anesthesia is employed.

Tissue harvesting causes a temporary disruption of positioning. If a general anesthetic is given for the harvesting, the patient can be allowed to awaken following completion of the harvest maneuver and,

thus, return to the regional anesthetic for sole maintenance. However, this necessitates the use of local anesthetic at the harvest site; otherwise, significant pain may occur following return to consciousness. Agents with short duration, such as alfentanil, are very valuable for the short general anesthetic.

The addition of music to the operating theater, or the use of a headset, has reduced the sedative needs of patients.⁴¹ White sound has a relaxing effect on most patients. Allowing the patient to have a choice also reduces sedative requirements, regardless of the music they choose. As importantly, room temperature must be kept at a reasonable level to prevent the patient's heat loss and shivering.

Intravenous Sedation

Reduction in patient anxiety with available drugs greatly enhances the success of regional anesthesia. Four categories of drugs are used: (1) narcotics; (2) barbiturates; (3) benzodiazepines; and (4) butyrophenones.

Narcotics serve to provide pain relief from sources other than the injured extremity. These drugs, when combined with an anxiolytic, produce a tranquil patient. The required dose varies between patients and should be titrated over the duration of the procedure. Morphine and fentanyl are excellent choices.

The anxiolytic effects of various benzodiazepines improve the experience for the patient. The compounds often produce amnesia. Furthermore, the antiseizure characteristics of this class of drugs reduces the possibility of local anesthetic-induced seizures. At present, the most popular benzodiazepine for purposes of sedation is midazolam, followed by diazepam. Diazepam alone may cause significant confusion in children, and barbiturates are preferred in younger children. The sedative effects of pentobarbital allow many patients to sleep through the replantation. This drug is titrated to effect and must be given on a regular schedule to achieve a smooth level of sedation. The butyrophenone, droperidol, has two effects: a neuroleptic and an alpha-blocking effect. When combined with a narcotic, the neuroleptic state leaves the patient quiet and resting for the procedure. The actual impact of the alpha-blockade on vessel size may be minimal. Droperidol can produce an alarming dysphoric reaction, with refusal of surgery, and it has a long duration of action. The use of droperidol (Innovar) to supplement regional blocks has decreased for these reasons. To avoid complete loss of consciousness and acid aspiration, sedative agents used to modify the patient's experience must be carefully titrated in small doses. No scheduled dose on a weight or age basis is suitable.

Fluid Management

Stated previously, isovolemic hemodilution is a method to reduce viscosity and improve blood flow without jeopardizing oxygen transport (see Figs. 3 and 4). Use of isotonic crystalloids to replace blood loss and measurement of serial hematocrit values to maintain a hem-

Table 1. *Method for Determining Maintenance Fluid Requirements in Children*

0-10 kg	100 ml/kg/24 hours
11-20 kg	1000 ml + 50/ml/kg/24 hours for each kg over 10
20+ kg	1500 ml + 20 ml/kg/24 hours for each kg over 20

From Smith R: Anesthesia for Infants and Children, ed 4. St. Louis, Mosby, 1980; with permission.

atocrit of 30 to 35 per cent accomplishes hemodilution. Colloid causes less tissue edema and is only given as an adjunct to crystalloid. Use of blood products may be necessary with continued blood loss. A recommended hematocrit of 30 per cent is arbitrary; the optimum value depends on the physical status and age of the patient. In children, lower hematocrits are well tolerated but, with decreased size, small amounts of blood loss may cause large shifts in the hematocrit. Care of children undergoing replantation requires special attention to fluid management. In addition to maintenance fluid requirements, we initially replace blood loss with crystalloid (Table 1). A predetermined hematocrit is chosen, especially in children, below which blood products are given to replace cell loss (Table 2). In our center, most patients receive red cells when the hematocrit levels decrease to below 30 per cent and, especially, if we anticipate continued loss. Placement of a central venous pressure cannula provides information about fluid requirements, but is not needed in all patients.

Communication

An essential element of a successful replantation is good communication between the surgeon, anesthesiologist, nurse anesthetist, and surgical nurse. The change of personnel, which occurs in long procedures, can easily lead to miscommunication. Each relief person must make an effort to acquaint himself with the status of the patient and projected time of completion of the procedure. The time of the

Table 2. *Example of a Method to Determine Acceptable Blood Loss in a 2-Year-Old Child Weighing 10 kg*

Estimated blood volume	$80 \text{ ml/kg} \times 10 \text{ kg} =$	800 ml
Normal red cell mass	$800 \text{ ml} \times 45\% =$	360 ml
Red cell mass at 30% Hct	$800 \text{ ml} \times 30\% =$	240 ml
Acceptable red cell loss		120 ml
Acceptable range of whole blood loss	$120 \times 2.2 =$	266 ml
	$120 \times 3.0 =$	360 ml

From Smith R: Anesthesia for Infants and Children, ed 4. St. Louis, Mosby, 1980; with permission.

original anesthetic and its anticipated duration should be common knowledge to each member of the team.

All team members must be thoroughly and rapidly informed about adverse changes in the patient. Individuals must work together in a cooperative, harmonious manner, especially when the case becomes tedious or patient status deteriorates significantly.

The Tourniquet

This article has not previously mentioned the potential damage from a tourniquet. During replantation, long periods of tourniquet inflation may be required. These times must be monitored to minimize tourniquet pressure and inflation duration, because both of these factors have been associated with nerve damage.^{32, 33, 41} The anesthesiologist or nurse anesthetist should periodically remind the surgeon about the inflation time. A tourniquet pressure exceeding systolic blood pressure plus 100 mm Hg should not be used.

Table 3. *Protocol for Anesthetic Management of Replants*

Triage
Concomitant injuries
Status
Fluids
Gastric contents
Coexistent disease
Treatment
GI
Metoclopramide
Ranitidine/Cimetidine
Sodium citrate
Volume replacement
Crystalloid
Colloid
Blood products (hematocrit <30%)
Anesthesia
Regional (first choice)
Axillary block
Interscalene block
General (second choice)
Maintenance
Rheologic state, isovolemic hemodilution
Warm room
Patient comfort
Position
Sedation
Anxiety
Communication
Anesthetist
Surgeon
Tourniquet
Time/pressure (minimal/lowest)

SUMMARY

Successful replantation requires a physiologically oriented team, including skilled surgeons with available relief and a skilled anesthesiologist with relief. Regional centers provide the most efficient management, having more frequent exposure to major injuries and increased experience with replant procedures. A management protocol (Table 3) outlines the major steps in the care of such patients. This author prefers regional anesthesia for most cases. Supplemental intravenous sedation reduces anxiety and its effects on the microvasculature. For axillary and interscalene brachial plexus blocks of the upper extremity, bupivacaine is most suitable. Management of lower extremity replantations usually entails a femoral sciatic, epidural block or a general anesthetic.

The anesthesia team must remember the importance of vascular physiology and rheology on outcome. Also, they must pay attention to (1) concomitant risks of emergency procedures (coexisting injury, intoxication, a full stomach, and so forth); (2) expeditious management, which reduces warm ischemia time; (3) patient comfort in the operating theater; and (4) a cooperative and informed team approach. Given these factors and proper patient sedation, a reasonable success rate can be expected.

In the future, advances in anesthesia care will involve better management of fluids and methods to prolong sensory and sympathetic blockade.

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Anesthesia for Temporomandibular Joint Arthroscopy

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Internal derangement of the temporomandibular joint (TMJ) is a frequent cause of facial pain and limitation of mandibular function. Internal joint derangements represent a specific pathologic condition of the TMJ and can be defined as an abnormal relationship of the articular disc to the mandibular condyle, glenoid fossa, and articular eminence.⁶ The disturbance results from mechanical displacement of internal joint structures and does not necessarily relate to pain or muscular imbalance. Surveys show that 10 to 25 per cent of the entire population have some degree or type of internal derangement of the TMJ.^{1, 7, 14} Women have a relatively high incidence of this problem; proposed mechanisms include (1) greater joint laxity, (2) an increased rate of collagen metabolism induced by hormones, and (3) a weaker musculoskeletal system.^{3, 8, 23, 37} Since 1887, the concept of anterior displacement of the disc has been suggested and equated with the signs and symptoms of jaw "clicking." Although initial clinical correlations were controversial, there now exists substantial evidence that this relationship does exist.^{16, 24, 46, 53, 54}

This article reviews the history of TMJ arthroscopy, presents the anatomy and pathophysiology of the TMJ, describes the operative technique and surgical requirements, and discusses anesthetic considerations for the procedure.

HISTORY

Orthopedic surgeons have used arthroscopy to examine joints for many years. Takagi⁴⁶ first described its use for knee examinations in 1918. The earliest report of its use in the West appeared in 1921.⁴ It was not until Watanabe and Takeda⁵¹ developed a smaller arthroscope (1969), that its use was fully established. In 1975, Ohnishi³⁶ first re-

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ported his use of the arthroscope to examine the TMJ. This prompted animal investigations to determine possible diagnostic and surgical applications.^{17, 55} Following this introduction, surgeons in Sweden began using TMJ arthroscopy for diagnostic purposes.²⁰ Although the basic principles of the technique were described, it was not until 1982 that Murakami and other workers^{30, 31, 33} provided a thorough description of the techniques of arthroscopic puncture and various intra-articular manipulations. Since that time, a number of reports detailing arthroscopy for the successful management of internal derangements of the TMJ have appeared in the literature.^{20, 32, 43, 44} Today, the use of TMJ arthroscopy has become a frequent procedure at many medical centers.

ANATOMY

The TMJ is classified as a ginglymodiarthrodial joint that has the unique capacity to allow both rotational and translatory movements (Fig. 1). The articular surfaces are covered with white fibrocartilage rather than by hyaline cartilage, which exists in most joints in the human body. An intervening disc divides the joint into a superior joint compartment and a smaller inferior joint compartment. The articular disc has been described as having four parts: a thick posterior band, a thin anterior band, an intermediate zone, and a posterior bilaminar zone⁴⁰ (Fig. 2). The thick posterior band runs across the head of the condyle converging medially and laterally to be inserted rigidly into the medial and lateral poles. Posteriorly, the meniscus splits to constitute the bilaminar zone. The upper lamina, which is made up of elastic fibers, is often incorrectly reported to assist in pulling back the disc like a rubber band when the mouth closes. It is the disc's attachments to the poles of the condyle that accounts for returning the disc. The upper surface of the disc is convex, accommodating to the form of the articular fossa and articular eminence. The disc's concave inferior surface remains in contact with the condyle of the mandible,

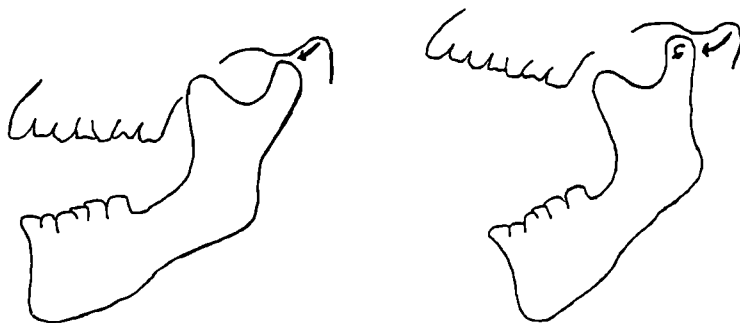


Figure 1. The normal TMJ has both rotational and translatory movements.

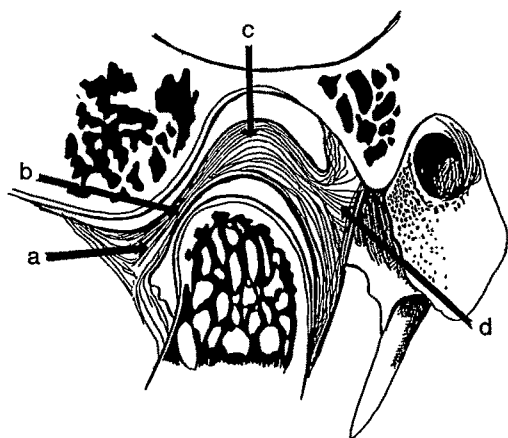


Figure 2. Anatomy of the TMJ. a, Anterior band. b, Intermediate zone. c, Posterior band. d, Posterior bilaminar zone.

and its circumference is connected to the fibrous capsule and also with the lateral pterygoid on its anterior aspect.

In the closed position, the transverse ridge of the articular surface of the condyle lies directly beneath the posterior band of the disc. On opening, the mandible initially drops downward and then rotates for the first 10 to 15 mm of opening. This rotational component of movement occurs in the lower joint space. As opening continues, the condyle rotates and the disc glides down the slope of the articular eminence. This translatory movement occurs in the superior joint compartment. The final component of movement occurs during maximal opening and also involves a rotational movement, which takes place in the lower joint compartment when the condyle moves onto or just in front of the anterior band of the disc. When the mouth closes the condyle moves in the reverse direction (Fig. 3).

PATHOPHYSIOLOGY

Frequently, clicking of the jaw is incorrectly equated with an internal TMJ derangement. Many audible clicks merely represent a transient disc-condyle-eminence incoordination. The click is often heard in the early phases of mandibular movement. Clicking occurs when the posterior band lies anterior to the transverse ridge of the condyle in the closed position and then relocates suddenly over the head of the condyle as the condyle moves forward on opening. For this subluxation to arise, the bilaminar zone and lateral attachment must be stretched or torn, resulting in the condyle taking up a more posterior and superior position in the fossa behind the posterior band. If the disc lies too far anteriorly, the condyle can no longer relocate itself on the disc (or become "recaptured"). This situation is termed "closed lock," because the disc is locked in a forward position.

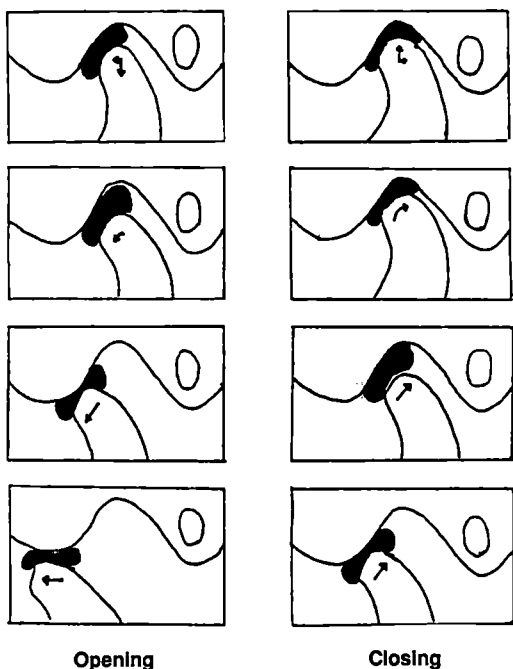


Figure 3. Movements that occur within the TMJ during mouth opening and closing. On opening the condyle rotates and moves downward and forward. The reciprocal motions occur during closing. The disc moves with the condyle during mouth opening and closing.

The etiology for internal derangement of the TMJ remains unproven. The theories for its occurrence can be divided into two subdivisions; macrotrauma and microtrauma. Macrotrauma can occur as a result of fractures, whiplash incidents, joint contusion, or iatrogenic trauma including the removal of third molars, intubation for general anesthesia, endoscopy, and tonsillectomy.³⁴ In these cases, most authorities suspected that a disruption of the lateral disc attachment occurs with stretching of the posterior attachment. As a consequence, disc displacement, intracapsular bleeding, and effusion results. Disc surface friction from an altered articular surface, fibrinous exudates, and a lack of joint lubrication may allow adhesions to form. These adhesions, most commonly seen in the superior joint compartment, trap the disc anteriorly, preventing normal physiologic movement. Because of this alteration in the internal structure of the joint, normal translation in the superior joint space is no longer possible. In addition, the anteriorly displaced disc forms a mechanical barrier preventing full opening. The disc misplacement places the highly innervated posterior bilaminar zone of the disc over the condylar head, producing pain directly over the joint. Muscular reflex arcs become activated from joint damage, and pain may also be elicited over the muscles of mastication.

Internal derangement resulting from microtrauma is harder to substantiate. It is thought that by altering normal transmission of the biomechanical load, the disc may be forced out of position into a more

Table 1. *Indications for Temporomandibular Joint Arthroscopy*

Diagnostic purposes
Pain and/or dysfunction of the joint
Enhancement of diagnostic findings prior to surgical management
Local tumor invasion into the TMJ
Investigation of TMJ relationships in systemic arthritides
Internal derangement
Persistent closed lock
Painful intermittent lock
Painful click
Arthrosis
Fibrous ankylosis
Postarthrotomy
Post-trauma
Presence of internal derangement and questionable joint pathology prior to complete prosthetic or orthodontic rehabilitation

anteromedial direction. Clenching and other parafunctional habits (for example, bruxism) that result in abnormal loading of the joint have been documented to be possible causes for disc displacement.⁹ Skeletal abnormalities such as retrognathia have also been implicated as predisposing factors for TMJ problems. Speech demands or other functional activity requiring excessive translatory excursions may, in part, place those with skeletal problems at risk. Arthrographic studies demonstrate a significant correlation between condylar hypermobility and disc displacements.³⁰ In all cases, an alteration in joint motion results in intracapsular damage, which changes the disc-condyle relationship in a manner similar to that with macrotrauma. Although the internal derangements in these patients are treatable, the predisposing factors (for example, psychological problems) leading to clenching or grinding must also be addressed; otherwise, permanent resolution of the problem may not be possible. With long-standing internal derangement, bony changes will also occur. Radiography commonly shows flattening and braking of the anterior surface of the anterior aspect of the condyle and subchondral sclerosis.

When presenting for arthroscopy most patients with TMJ disorders are able to open their mouth adequately. However, these individuals have the potential to develop TMJ locking, with subsequent difficulty in airway management.^{39, 49} Dislocation of the TMJ after direct laryngoscopy can also be encountered.¹⁰

There are many different TMJ disorders, and arthroscopy can be useful in establishing the diagnosis and can be used as a therapeutic maneuver in a number of these conditions (Table 1).

OPERATIVE TECHNIQUE

TMJ arthroscopy is usually performed in the outpatient operating room. After induction of general anesthesia, the surgeon has the op-

portunity to assess joint function and range of motion. There are several different approaches advocated to arthroscopically enter the joint, including the inferolateral, posterolateral, superior anterolateral, inferior anterolateral, and endaural approaches.^{29, 33, 51}

The arthroscopic technique begins while the surgeon manipulates the mandible downward and forward. This is done to open the joint maximally. The surgeon then inserts a 20-gauge needle into the superior joint compartment and slowly injects heparinized lactated Ringer's solution to gently distend the joint. This allows easy trocar puncture and minimizes the risk of iatrogenic intracapsular damage. An 18-gauge "outflow" needle with attached tubing is then introduced into the anterior aspect of the superior joint compartment. Slow injection of iced, heparinized lactated Ringer's solution through the outflow needle re-establishes joint distension. The arthroscope cannula with a sharp trocar is then used to enter the superior compartment. Once properly positioned, the trocar is removed and the arthroscope is placed via the cannula (Fig. 4). With the arthroscope, the surgeon visualizes the superior joint compartment and then systematically examines the entire joint. The arthroscope or blunt probe can be used to sweep the superior compartment to lyse adhesions, perform a synovectomy, or proceed with partial menisectomy. The joint undergoes continuous lavage during the procedure. The external auditory canal and tympanic membrane are examined at the end of the procedure to assess possible trauma to the canal.

The duration of surgery depends upon operator, but the technique



Figure 4. Lateral view of patient. A needle is introduced into TMJ joint and the joint is distended with iced solution. An index finger palpates the depression over the joint as the mandible is manipulated downward and forward.

commonly lasts for 10 to 30 minutes per TMJ. At the end of the procedure, the puncture wounds infrequently require suturing. Placement of a small bandage over the puncture site usually suffices. We discharge patients directly from the recovery room to the physiotherapy department for treatment. In a majority of individuals, acetaminophen with codeine provides adequate control of postoperative pain.

Potential Surgical Complications

All members of the anesthesia team must be aware of the potential surgical complications, because they may be asked to evaluate these difficulties postoperatively. Problems mainly involve the structures near the operative site. Because the facial nerve and the superficial temporal vessels are extremely close to the TMJ, these structures are at risk. Local anesthetics that are injected into or near the joint can cause occasional temporary seventh nerve palsy.¹⁵ Bleeding from a branch of the superficial temporal artery can occur,¹¹ and injuries to the middle ear or postoperative middle ear infections have also been reported.^{44, 50} Although unlikely, the most severe complications include carotid artery perforations and the potential for the trocar piercing into the middle cranial fossa.

ANESTHETIC CONSIDERATIONS

Preoperative Evaluation

A thorough history and physical examination is essential. Careful assessment of functional integrity and range of motion of the TMJ can prevent airway surprises following anesthetic induction. The oral cavity should be evaluated, and abnormal anatomy, poor dentition, or other factors that may influence intubation should be noted. A thorough physical examination of the TMJ includes palpation anterior to the tragus as the patient opens and closes the mouth. The initial movement felt should be rotational for the first 15 mm of mouth opening, followed by a secondary gliding movement. If only the rotational motion is noted, the anesthetist may well experience difficulty in opening the mouth widely for intubation. In the average adult, the mouth should be able to open 40 mm or more.⁵

Choice of Anesthesia

The initial report by Ohnishi³⁶ had patients seated in a dental chair while TMJ arthroscopy was performed, with local anesthesia and nitrous oxide for sedation. However, most patients are reluctant to undergo the procedure with this approach, because it allows unnecessary pain even for the most stoic individual. Thus, the local with nitrous oxide method can make the patient uncomfortable and uncooperative, and the surgeon can find it difficult to manipulate the mandible during surgery. General anesthesia provides complete pain relief during the procedure as well as complete muscle relaxation,

allowing unrestricted movement of the mandible. Therefore, all patients in our center receive general anesthesia for this procedure.

Induction of General Anesthesia

Nasal intubation is preferred over oral intubation because the jaw needs to be free for manipulation and assessment of occlusion. In our practice a nasal RAE tube is the least obtrusive method to secure the airway. When physical examination indicates that intubation should not be difficult, then we proceed with anesthetic induction, placing the nasotracheal tube under general anesthesia. If there is any question about the ability to intubate the patient, however, awake intubation by either the blind nasal approach or fiberoptic bronchoscopy precedes full induction of general anesthesia. Awake intubation techniques have been well described^{19, 26, 42} and will avoid morbidity in patients presenting with an abnormal airway.

After pre-oxygenation, a short-acting barbiturate is used for induction, the ability to ventilate is established, and then the patient is paralyzed with either succinylcholine or a nondepolarizing muscle relaxant (Table 2). We prefer atracurium or vecuronium, when a nondepolarizing agent is selected, due to the shorter duration of action.

The most frequent complication of nasal intubation is epistaxis. To decrease the incidence of this, oxymetazoline 0.05 per cent (Afrin) is sprayed into each nostril for vasoconstriction prior to intubation. Alternatively, topical cocaine or phenylephrine may be used, but neither has been shown to offer significant advantages over oxymetazoline.^{27, 28} In comparison to cocaine, oxymetazoline is less expensive and is more readily available because it is a noncontrolled drug. Sequential dilation with lubricated nasal airways also decreases the incidence of nasal trauma.^{21, 38} Topical lidocaine has been shown to

Table 2. *Anesthetic Plan*

Induction
Preoxygenation
Thiopental/ventilation established*
Nasal spray with topical vasoconstrictor
Muscle relaxation/lidocaine laryngotracheal anesthesia
Intubation with a warmed nasal RAE tube
Tube secured to head-wrap
Maintenance
Ventilation controlled
Muscle paralysis assessed with peripheral nerve stimulator
Succinylcholine drip or incremental nondepolarizing muscle relaxants
Inhalational anesthetic (eg, N ₂ O/O ₂ , isoflurane)
Conclusion
Muscle paralysis reversed
Spontaneous ventilation established
Extubate deep

* Airway assessment consistent with the ability to intubate, otherwise awake intubation performed.

blunt the hemodynamic responses to nasal intubation.¹³ Lidocaine jelly, 2 per cent, or ointment, 5 per cent, provides both topicalization and lubrication. An additional and often helpful technique to prevent epistaxis with nasal intubation is to warm the endotracheal tube prior to intubation.²⁷ We accomplish this by submerging the distal end of the nasal RAE tube into a bottle of heated normal saline. Clinicians have used a blanket warmer to soften endotracheal tubes, yet in our experience this can cause the full length of the tube to become excessively soft and difficult to manipulate. Smaller endotracheal tubes may also be advantageous, and we recommend a 6-mm ID endotracheal tube for women and a 7-mm ID tube for men. The airway resistance of small endotracheal tubes does not appear to be a problem as the patient is intubated for a short duration and ventilation is controlled for most of the case. The use of a fiberoptic bronchoscope may necessitate use of a larger diameter tube.

Because of the normal bevel of the standard endotracheal tube, the right nostril is intubated if possible. This allows the bevel of the endotracheal tube to slide along the septum, avoiding trauma to vascular mucosa of the nasal turbinates. If the left nostril is used, the tube should be reversed (that is, with the normal curve of the endotracheal tube facing the anesthetist), maintaining the bevel toward the septum; after entry into the posterior pharynx, the tube is rotated 180 degrees and advanced into the trachea. If needed, the use of direct laryngoscopy allows the anesthetist to guide the tip of the tube into the trachea, sometimes using Magill forceps. Using direct laryngoscopy to visualize the cords has not been shown to exacerbate TMJ disorders, but gentleness is still warranted.⁴⁹

Because the head and TMJ will be manipulated intraoperatively, one must have the endotracheal tube and airway hoses well secured. The tubes can be secured to the forehead or a head-wrap or both. Several reports^{12, 45} describe the use of devices that incorporate Velcro attachments to facilitate fixation. In the process of securing the nasotracheal tube, care must be taken to avoid excessive pressure on the nasal alae; otherwise, pressure sores may develop.

Monitoring

In addition to the standard monitoring used for general anesthesia, routine use of pulse oximetry and end-tidal CO₂ is recommended. An esophageal stethoscope, placed through the nonintubated nostril, or a precordial stethoscope can be used to monitor respiratory and cardiac sounds during the procedure.

Positioning

To allow the surgeon and assistant access to either side of the head, we turn the table 90 degrees from the standard position. Others¹⁵ tilt the table to each side so the operative joint is in the horizontal plane. Six-foot airway circuit hoses allow the anesthetist to position the anesthesia machine at his or her side and away from the head of the table. Placing one arm on an arm board allows the placement of

a peripheral nerve stimulator over the ulnar nerve, near the anesthetist. A disposable foam circle (donut) can be used to stabilize the head.

Supplemental Agents

After the insertion of an intravenous catheter, prophylactic antibiotics are administered to prevent wound infections. Steroids are also given to help prevent edema and postoperative swelling. Narcotics are usually not given intraoperatively because postoperative pain is minimal, and narcotics can prolong discharge times in outpatients. To reduce postoperative nausea and vomiting, small doses of droperidol (Inapsine) can be given prophylactically or after nausea develops. Prior to oral cavity manipulations, we administer glycopyrrolate (Robinul), 0.2 to 0.4 mg IV, to minimize oral secretions. Because patients fast overnight prior to surgery and frequently have decreased oral intake after surgery, adequate IV fluid replacement is important.

At the end of the operative procedure, muscle relaxation is reversed and spontaneous ventilation established. Bucking or straining can cause bleeding into the surgical site, which can be prevented by extubation while the patient remains deeply anesthetized. However, if any question exists regarding adequate airway control, extubation is deferred until the patient awakens. The prior use of laryngeal tracheal anesthesia may help prevent intubated patients from coughing during emergence. Intravenous lidocaine, 1.5 mg per kg, also helps to suppress the cough reflex. In summary, if the preoperative examination demonstrates adequate range of motion and mouth opening, we anesthetize the patient and then intubate; but, if there is any question about airway patency we opt for an awake intubation. Similarly, at the end of the procedure, the patient with a normal airway frequently receives extubation while deeply anesthetized, whereas the individual with a difficult airway remains intubated until awake.

SUMMARY

TMJ arthroscopy is a new diagnostic and therapeutic modality added to the armamentarium of oral and maxillofacial surgeons. The procedure allows direct vision of the joint and provides information about the articular surfaces that is frequently not available by other diagnostic methods and is an excellent method for differentiation of TMJ disorders.

Over time, arthroscopy of the knee joint has replaced open arthrotomy, and similarly, TMJ arthroscopy has the ability to replace previously used diagnostic and therapeutic modalities of the TMJ. It is not only a diagnostic procedure but can be therapeutic as well. Internal derangement with persistent closed lock and arthrosis with adhesive capsulitis are examples of problems where arthroscopy can be utilized as a therapeutic procedure.

The anesthetic requirements include complete relaxation of the joint, a secure airway that minimally interferes with the joint, main-

tenance of head and TMJ mobility, and rapid recovery so the patient can pursue physiotherapy soon after the procedure. A knowledgeable team of anesthesia personnel and oral surgeons with good communication will facilitate the care of the patient.

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Anesthesia for Magnetic Resonance Imaging

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For years, physicians' needs to peer inside the human body from the outside were met by conventional radiography. Unfortunately, this technique did not allow the discrimination of overlapping structures. Computerized tomography (CT) has provided further discrimination of the anatomy of the body by utilizing radiographic data recorded from multiple directions and by reconstructing the data mathematically to create an image. Although CT scanning has provided excellent anatomic pictures, it also has its shortcomings. It provides no insight into the function and physiologic state of internal organs, and it carries a finite, albeit small, risk of exposure to ionizing radiation.

Magnetic resonance imaging (MRI, previously called nuclear magnetic resonance) is a new technique for obtaining both an anatomic and functional picture of the human body. The technology has been available since 1952 when Felix Bloch of Stanford University and Edward M. Purcell of Harvard University were jointly awarded the Nobel Prize for physics. The theory behind MRI is based on the knowledge that certain nuclei have intrinsic magnetic properties and, when placed within a magnetic field, they can be made to absorb or emit electromagnetic radiation.^{8, 10, 16, 17} This property of all biologic atoms is exploited to create high-contrast images of the human body.

The major problems for the anesthesiologist asked to provide care for patients undergoing this procedure are created by the constraints of the magnetic field. The goal of this article is to outline the principles of the operation of MRI, because only through an understanding of the technology can the anesthesiologist appreciate the limitations that these constraints place on the provision of safe anesthesia. In addition, methods of patient monitoring and safety are discussed, and techniques of providing anesthesia are suggested. Lastly, MRI technology is also being used to provide information into cellular physiology and to investigate the kinetics of brain binding with inhalation agents. A brief overview of the current scientific knowledge is presented.

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PRINCIPLES OF MAGNETIC RESONANCE IMAGING

MRI is a diagnostic technique that employs a strong magnetic field and radiofrequencies (RF) to generate images.^{8, 10, 16, 17} When the nuclei of certain atoms are placed within a magnetic field and then stimulated by radio waves of a particular frequency, they re-emit some of the absorbed energy in the form of radio signals. To understand the principles fully, a knowledge of quantum mechanics and Fourier transformation is necessary. This is obviously beyond the knowledge and interest of many anesthesia practitioners (including the author) and, thankfully, the scope of this article. What follows is a much less ambitious explanation. Those interested in a more detailed explanation are referred to several articles.^{16, 17, 23}

In general, atomic nuclei contain both protons and neutrons, the exception being the hydrogen nucleus (^1H) which consists of a single proton. All nuclei possess an intrinsic angular momentum, or "spin"; however, pairs of protons or neutrons will balance themselves in such a way as to cancel out any net spin. Therefore, only nuclei with an odd number of protons are MRI responsive; the principle ones of biologic interest are the hydrogen nuclei (protons), ^{31}P , ^{23}Na , and ^{13}C . Because these nuclei have an associated electrical charge distribution, the net rotation or spin generates a magnetic field. In the absence of any applied external field, the orientation of these nuclei is random. In the presence of a uniform magnetic field, these nuclei will act like bar magnets and align themselves in a longitudinal direction or parallel to the magnetic field.

The MRI system utilizes a large bore magnet that has the shape of a cylinder capable of surrounding the human body (Fig. 1). In the tube is an RF transmitter coil that also surrounds the patient and acts as a receiver to detect the MRI signal. To induce the nuclear resonance phenomenon, a short RF pulse is applied via the transmitter coil. If the frequency of rotation is appropriately chosen (each given atom will have its own specific frequency), the aligned nuclei will experience a torque that displaces the net axis 90 degrees from the parallel position into a horizontal plane. When the pulse is discontinued the magnetization relaxes back to the longitudinal axis. It takes a specific length of time for the recovery to occur, and this constant time interval is termed T1 (or spin-lattice relaxation time). During this time period, an electrical signal is captured in the receiver coil. Relaxation of the magnetization in the transverse direction back to its original value is characterized by another time constant termed T2 (or spin-spin relaxation time).

The signal detected after a 90-degree RF pulse is called the free induction delay, and it is this signal that is used to reconstruct the image. Recovery times (T1 and T2) are sensitive indices of local nuclear and molecular environments, and these inherent tissue properties are used to distinguish between normal and abnormal tissues.

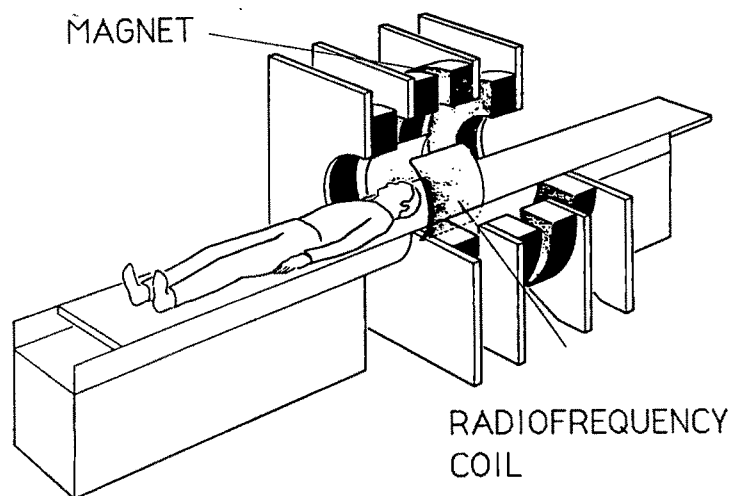


Figure 1. Schematic diagram of a patient in the MRI scanner. The diagram illustrates how the magnet and radiofrequency coil surround the patient.

Nuclei of a particular MRI-responsive atom will respond only to stimulation by an RF pulse of a specific frequency known as the Larmor frequency. The response is directly proportional to the strength of the static field, so that if a patient is placed in a gradient magnetic field, a certain frequency will define a finite distance along the body. Then, using a three-dimensional system, spatial labeling is obtained and the body image can be scanned by successive cuts (a computer reconstructs the image much like CT scanning).

The resolution of the image depends on the strength of the magnetic field, which is typically 0.5 to 1.5 T (1 T = 10,000 G). At the UCSD Medical Center we currently employ a General Electric Signa scanner that operates at 1.5 T. To put that number into perspective, the magnetic field around the earth is about 0.6 G. Certainly, a magnetic field of 1.5 T has enough magnetic pull to create havoc for the anesthesiologist as well as potential danger to the patient (for example, displacing clips off aneurysms). Currently, most MRI systems use the hydrogen nuclei (protons) for biologic scanning. This is convenient because of the body's high water content and abundance of hydrogen nuclei.

Unfortunately, to prevent imaging artifacts, patients are required to remain still during the cuts (Fig. 2). Unlike CT scans in which the cuts are seconds long, the patient is required to remain still for successive 15-minute cuts often up to 1 hour. Although most adults are capable of this, many patients who require MRI scanning may have an impaired level of consciousness. Also, small children likely require either sedation or general anesthesia to prevent any motion artifacts.



Figure 2. Photograph of a patient on the scanning pallet prior to entering the scanner. Because of the depth of the machine, the entire patient is obscured from view during a body scan.

ANESTHETIC CONSIDERATIONS

Anesthesia Equipment

Early MRI spectroscopy focused on imaging the brain, but like CT scans they are now being used to image many anatomic structures and body cavities.^{8, 10, 15, 23} Initially, only healthy adults were scanned, but as the need for physiologic information grew, patients of all ages and physical conditions required MRI. Their increasingly complicated medical histories more frequently warrant the involvement of anesthesia personnel.

The major constraints facing the anesthesiologist who provides services in the MRI suite are created by the magnetic field and the physical structure of the machine itself. The main problems include airway management, relative inaccessibility to the patient, monitoring, and environment changes (Table 1).

Within the MRI suite, and certainly near the bore of the magnet, all ferromagnetic components need to be avoided. The magnet is extremely powerful and creates three important problems that impact on anesthetic management. The first is that any ferromagnetic object that approaches the magnet has the potential to be hurled toward the scanner, creating a lethal projectile. The second problem is that many large metal objects (even nonferromagnetic) have the potential to interfere with the scanner and degrade the image. Third, a wide variety

Table 1. *Problems Encountered in the Magnetic Resonance Imaging Suite*

Anesthesia
Choice of technique
Patient accessibility
Scanner noise
Equipment modifications
Manpower utilization
Patient safety: vascular clips, pacemakers, etc.
Monitoring
Image degradation
Monitor function
Vibration sensitivity
Environment
Remote location
Cold room, hypothermia in infants
Recovery location

of electronic instruments and monitoring devices will not function properly within the vicinity of the magnet.

Almost all anesthesia equipment that is metallic contains some ferrous-bearing material, although the amount differs from device to device. Therefore, the degree of magnetic pull varies with each instrument; the higher the ferrous content, the greater the attraction toward the scanner within the magnetic field. Therefore, objects that we use daily need to be modified to permit their use, or suitable alternatives need to be found. A number of authors have looked at commonly used equipment and offered suggestions about their modification (Table 2).^{2, 7, 13, 18, 22}

The first concern of most anesthesiologists is airway control, and much of the airway equipment we use contains ferrous material. This begins with the laryngoscope. Although the laryngoscope handle and blade are nonferromagnetic, the batteries inside are strongly magnetic, making the entire apparatus unwieldy in the MRI suite. If no alternatives to endotracheal intubation are possible (for example, use

Table 2. *Ferromagnetic Materials That Need Substitutions*

Ventilator
Gas cylinders
Laryngoscope batteries
Tracheal tube connectors
Magill forceps
Stethoscopes
Scissors
Butterfly needles (Abbott)
Gurneys
Wheelchairs
IV poles
Personal items (see text)

of a natural airway), then laryngoscopy can be performed with conventional equipment outside of the scanning room. Also, to remedy this situation, either plastic-covered batteries can be purchased and substituted in the laryngoscope handle for standard batteries, or the standard batteries can be covered with a paper casing (this markedly decreases their pull to the machine). Other equipment such as patient gurneys, intravenous poles, and so forth, can easily be constructed out of nonferrous alloys and dedicated for use in the MRI suite.

Perhaps the most difficult piece of equipment to modify is the anesthesia machine itself. Several parts of the anesthesia machine contain ferromagnetic materials including the gas cylinders, vaporizers, and ventilator. Anesthesiologists in several institutions have tried different ways to solve this problem. Some have physically situated the machine outside the scanning room and extended the breathing circuit through a break in the wall, to reach the patient. This method is cumbersome, difficult to accomplish, and requires at least two people to administer the anesthetic. An alternative approach places the machine within the MRI suite but as far away from the magnet as possible and bolted to the wall. This allows for the use of inhalation agents and controlled ventilation. Whether or not the machine will degrade the images has been highly variable, depending on the magnetic field at the individual centers. Several locations within the suite have to be tested to identify the appropriate place. The economic feasibility of designating an anesthesia machine for the MRI suite depends on the case load. Currently, at our institution, the frequency of cases varies between 2 to 6 per month but seems to be increasing, as MRI scans are proving to be the diagnostic mode of choice in many new situations.^{15, 22}

Recently, a ventilator (225/SIMU R ventilator, "MRI compatible," Monaghan Medical Corporation, Plattsburg, NY) has been developed that reliably ventilates patients during an MRI scan.^{5, 22} The manufacturer states that the ventilator has been modified to eliminate virtually all ferromagnetic materials by substituting them with aluminum or other nonferrous alloys. The ventilator is pneumatically driven (compressed oxygen at 50 pounds per square inch gauge [psig] from a standard hospital wall unit) and controlled entirely through the use of fluidics. Appropriate testing by the manufacturer and others reveals that it functions without image degradation in a magnetic field of up to 1.5 T.

At our institution, we have a large H cylinder of oxygen positioned outside the MRI room, with a valve outlet in the room because we have no pipeline source available. Therefore, the use of a pneumatically driven ventilator would have some time limitations. We currently employ a modified bain circuit when controlled ventilation is necessary, but this set-up precludes the management of critically ill, ventilator-dependent patients (Fig. 3). At the same time, the literature is beginning to demonstrate that MRI is the preferred diagnostic method in many medical conditions and is particularly useful following acute head trauma in patients with possible increased intracranial



Figure 3. Modification of the bain circuit. The fresh gas flow tubing is lengthened with plastic connectors to reach the gas source. The airflow is regulated by adjusting the valve from an open to semi-closed to closed position.

pressure. Therefore, our inability to provide controlled ventilation presently excludes a significant number of patients from receiving this beneficial service. We plan to test and purchase an "MRI-compatible" ventilator, which will extend our services to critically ill patients.

It is quite important that patient care personnel keep ferromagnetic materials outside of the scanning room. If brought within the scanner environment and if not tightly secured, these objects will truly become projectiles, achieving maximum velocity at the center of the magnet where the patient is lying. Certain pieces of equipment cannot be replaced by nonferrous materials; thus, no suitable alternatives exist (for example, gas cylinders). They must be kept and used outside the scanning environment (as described previously). Of lesser importance, some personal items are affected by the magnet and should be left outside of the scanning room. For instance, the magnetic information on credit card strips will be erased, analog watches will cease to function, and beepers may become inoperative.

Monitoring Devices

As mentioned previously, three major obstacles confront the anesthesiologist who attempts to monitor the patient: (1) image degradation from the monitors; (2) noise/vibration sensitivity within the scanner; and (3) the ability of the monitor to function reliably within the MRI suite. Direct observation of the patient is impossible because the body cylinder of the scanner totally surrounds the patient (especially children). Therefore, the need for good patient monitoring assumes increased importance. Table 3 lists some monitoring solutions for patients in the MRI suite.

The first substantial problem is how best to monitor the patient's cardiac rhythm. Conventional ECG monitoring is not possible,

Table 3. *Monitoring Alternatives to Standard Equipment*

Electrocardiograph
Telemetry, vascular Dopplers, palpable pulse, plastic precordial stethoscope
Blood pressure
Automated blood pressure cuff (Dinamap 1846, Omega 1400), revised manual system
Ventilation
Apnea alarm mattress, chest bellow, pulse oximeter (Biochem Microspan 1040), capnograph (Biochem 515), plastic precordial stethoscope

because the lead wires traverse the magnetic field causing both ECG distortion, as well as decreasing scan quality. Several approaches can ameliorate this problem. At our institution, we have installed telemetric ECG monitors (with RF filters to decrease interference from the scanner.) An oscilloscope, mounted outside the viewing window over the control console, can be turned to face inward where it can be seen by the anesthetist in the scan room. This works reasonably well, although the scanner sometimes distorts the baseline so much that the cardiac rhythm becomes unreadable. For that reason, back-up methods have to be available. Vascular Doppler systems allow anesthesia personnel to hear the pulse when it is not palpable or within reach. The use of a plastic esophageal or precordial stethoscope represents an alternative method to monitoring the cardiac rhythm, although the sounds can be drowned out by the noise of the scanner.

The next major monitoring problem focuses on a method for determining the blood pressure. A sphygmomanometer can be constructed by replacing most of the ferromagnetic material with plastic and alloys. It should be kept as far away from the magnet as possible. Occasional erratic readings are possible as the needle may stick during cuff deflation. We have tested several different automated blood pressure devices that use oscillometry (see Table 3) and have had good results. We use the standard Dinamap 1846 XT (Critikon Inc., Tampa, FL) that is currently employed in the main operating room. To prevent imaging artifacts, the machine rests in the corner of the MRI room. This requires that the tubing is lengthened with plastic connectors that enable it to reach the patient. Improper function of automated devices has been reported and probably results from malfunction of the solenoids, which contain some ferrous content, and subsequently stick within the magnetic field. Prior to each case, selected equipment should be tested within the magnetic field, and alternatives should be readily available.

Because the patient may be hidden from view, it may be difficult to ensure adequate ventilation. A variety of suggestions have been offered by the authors referenced.^{2, 7, 13, 18, 22} These include the use of a plastic esophageal or precordial stethoscope, an aneuroid chest bellow, and an apnea alarm mattress. We have successfully measured oxygen saturation in our MRI suite with a specifically designed MRI-

compatible instrument (Microspan 1040, Biochem International Co., Waukesha, WI). The Nellcor-100 oximeter did not function reliably and, in one instance, may have been damaged (input amplified transistor destroyed and required repair). Biochem International also markets a capnograph (Biochem 515) that appears to function most of the time. This is actually a respirometer that counts breaths per minute and does not give a quantitative CO₂ reading. Unfortunately, none of these monitors has a "perfect track record," and can malfunction or give erratic readings during scanning periods.

If an emergency situation occurs, the magnetic field can be discontinued to allow for more accurate monitoring equipment and standard resuscitative methods (note that when the magnet is turned off a period of 1 to 3 hours is required before it can become functional again). Anesthesia personnel should familiarize themselves with the operation of the sliding platform to facilitate extrication of the patient in an urgent situation. A standard defibrillator and resuscitation cart should be located near the scanning room and checked routinely, so that resuscitation can begin immediately if needed.

Anesthetic Management

The preferred approach to anesthesia in the MRI suite depends on a number of variables. These include patient age and coexisting medical problems, the facilities and equipment present (for example, is a ventilator available?), and the type and intended duration of the scan. To prevent imaging artifacts, patients are required to remain still for 15-minute cuts, and any significant movement during these individual periods will necessitate reduplication of the entire process. Other factors to consider when choosing the anesthetic are accessibility to the patient and airway as well as the loud rhythmic noise emitted by the scanner.

To date, children and uncooperative adults (for example, some mentally retarded) have accounted for the majority of our patients. The first decision to make is whether or not the patient will require general anesthesia or can be adequately managed with intravenous sedation. In most institutions, as at UCSD, radiologists have their own protocol for giving sedative medications to both children and mildly uncooperative adults, and we are not asked to "stand by." When we are asked to provide services, the anesthesia team can still use monitored anesthesia care with intravenous sedation if appropriate. Regardless of method chosen, airway maintenance in an "avoid-the-surgical-field" situation constitutes the most worrisome problem. This may push some anesthesiologists to intubate all of their patients, and thus routinely administer a general anesthetic. Nixon and others¹³ advocate this approach. However, we have been able to complete a majority of cases with either intravenous sedation or general anesthesia with spontaneous ventilation and a natural airway. This undoubtedly reflects the fact that there is no MRI-compatible ventilator presently available at our institution.

Prior to the use of general anesthesia or intravenous sedation, it

is important to establish good intravascular access, not only for the administration of anesthetic agents but for emergency purposes. In children we usually administer ketamine (3 to 7 mg per kg) and an anticholinergic (glycopyrrolate or atropine) intramuscularly. This dose of ketamine "stuns" the child and allows us to insert an intravenous catheter while observing the child's ventilatory pattern. We specifically look for evidence of airway obstruction, the presence of copious secretions, or any other indication for endotracheal intubation. If endotracheal intubation is needed, then the depth of anesthesia is increased, which allows the patient to tolerate the endotracheal tube without moving. If intubation is not necessary we keep the dose of intravenous agents, especially narcotics, to a minimum, attempting to have patients breath spontaneously, with a natural airway (Table 4).

After intravenous access is established, sufficient sedation is given, and a patent airway is secured, the patient is moved into the scanner room. The patient is placed on the sliding platform, and oxygen is administered via a face mask. We then apply the appropriate monitors: a precordial stethoscope, telemetric ECG, automated blood pressure machine, pulse oximeter, capnograph, and temperature probe. If all equipment functions properly, we then direct our attention to heat preservation, trying to keep the patient's temperature as normal as possible. Infants are wrapped in warm blankets to prevent radiant heat loss. The scanning room and machine pallet is often cold, and infants will cool rapidly if precautions are not taken for prevention.

This initial process usually requires about 10 to 20 minutes. During this time the need for an artificial airway should be constantly reassessed (many patients require either an oral or nasal airway). When the intramuscular ketamine used for induction in children begins to remit, we maintain anesthesia with intravenous agents such as ketamine, a short-acting barbiturate (thiopental or methohexital) or with intravenous midazolam (see Table 4). A modified bain circuit is always present so that if the patient's airway deteriorates, endotracheal intubation and controlled ventilation can be instituted. Over 90 per

Table 4. Suggested Anesthetic Technique for Children

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1. IM ketamine (3–7 mg/kg) with IM glycopyrrolate (0.05–0.1 mg) or rectal methohexital (15–25 mg/kg). Apply standard monitors and oxygen
 2. IV placement
 3. Assess airway for need for endotracheal intubation
 4. Transfer child into room, reapply monitors and oxygen, wrap in blankets, reassess airway patency and adequacy
 5. Maintenance with IV ketamine (0.5–1.0 mg/kg) or incremental doses of sodium thiopental (1–2 mg/kg) or incremental doses of midazolam (0.03 mg/kg) to a maximum dose of 0.1 mg/kg
 6. Recovery dependent on set-up; may need monitored transport to main hospital recovery room
-

cent of patients tolerate this technique without requiring endotracheal intubation. In only one instance have we had to intubate the patient after the scan had begun.

This anesthetic technique is unacceptable for patients with increased intracranial pressure, such as those with a closed head injury or tumor. In these individuals, we induce anesthesia with a barbiturate, paralyze the patient with a nondepolarizing neuromuscular blocker, administer intravenous lidocaine, then intubate the trachea. Moderate hyperventilation can be accomplished with the use of the Bain circuit and high fresh gas inflow rates to prevent rebreathing and hypercarbia. Anesthesia is maintained with a combination of muscle relaxant, narcotic, and a thiobarbiturate, with the intent of avoiding a large dose of any single agent. Intracranial mass lesions truly dictate mechanical ventilation to ensure hyperventilation and hypocapnia, and to avoid an increased intracranial pressure.

Post-Treatment Care

A problem often exists regarding where and how to recover the patient. Because most scanners are located in remote environments (for example, ours is three blocks away from the main hospital) there is usually no adequately trained personnel, other than the anesthetist, to watch the patient during emergence from the anesthetic. Manpower utilization usually mandates transferring the patient from the MRI suite to the main hospital recovery room. At our institution, this is accomplished with the aid of an ambulance service. Patients are then observed in the recovery room until they are "street fit" or, in the case of in-hospital patients, meet the criteria to return to their rooms. If patients are intubated we usually transport with the endotracheal tube in place, and then perform extubation in the comfort of our own environment.

It is important to emphasize that the method of management described is far from perfect and is a suggested anesthetic technique that may require modifications. For us, it works relatively well given the limited equipment presently available. Surely, an inhalation anesthetic with a potent volatile agent or a narcotic-relaxant technique would work equally well and perhaps better, if that option were available. Clearly, with the development of improved MRI-compatible devices, such as a mechanical ventilator, the choices for providing a safe anesthetic will increase.

PATIENT SAFETY

A major advantage to the patient and personnel is that MRI scanning does not involve the use of ionizing radiation. However, three distinct sources of potential hazard to the patient exist: (1) the static magnetic field; (2) the changing magnetic field gradients; and (3) the RF field. At present, authorities generally accept that static fields have

no reproducible adverse effects on living tissues below 2 T (most systems use 0.5 to 1.5 T). The U.S. Bureau of Radiological Health suggests that this level should not be exceeded.^{4, 13, 19} However, the static magnetic field can be hazardous to patients with implanted ferromagnetic devices.^{3, 12, 14}

Cerebrovascular clips have a varying degree of ferromagnetic content. In the study by New and Rosen,¹² 16 of 21 intravascular clips were deflected by the static magnetic field. Five of the 16 were deflected by more than 46 per cent, an amount that creates a significant risk of dislodgement. This raises the potential of hemorrhage from a clipped cerebral aneurysm or injury to adjacent brain tissue. The degree of risk depends on a number of factors that include the degree of ferromagnetism, the geometry of the clip, and the degree of torque from the field. These risk factors are difficult to assess for the individual patient. Therefore, we currently exclude any patient with vascular clips, unless the metal content of the clip is well documented. It is interesting to note that the newer surgical clips are composed with a higher nickel content, so that this may not be an issue in the future.

The static magnetic field can also affect pacemakers.¹⁴ When a demand pacemaker is evaluated, a magnet of about 0.1 T is often held over the unit to close a reed switch, thereby bypassing the sensing system and converting the pacemaker to the asynchronous mode. Hence, demand pacemakers within the magnetic field will revert to asynchronous operation as a result of reed switch closure. Also, the casing of older pacemakers may be composed of stainless steel and, when exposed to the magnetic field, can be rotated or displaced. In addition, RF levels present within the MRI suite may confuse or possibly inhibit demand pacemakers, although the sensing circuitry itself is not involved. Lastly, time-varying magnetic fields can induce an electric current, which may be mistaken by the pacemaker as natural electrical activity of the heart, and thus inhibit output. Therefore, we currently exclude patients with pacemakers at our institution.

Davis and coworkers³ reported that the changing magnetic and RF may cause localized tissue heating effects in metal surgical clips and larger implantable prostheses. They found no significant increases in temperature due to the presence of copper or steel clips. However, a relatively large increase in temperature occurred when two hip prostheses in a saline solution were exposed to the changing fields. They surmised that this related to the large conducting paths created by the saline solution and most likely would not be a problem *in vivo*.

In summary, to prevent possible injuries, we presently exclude all patients with surgical clips of unknown content and those patients with pacemakers (without the approval of the cardiologist), but do allow patients with a nonferromagnetic metal prosthesis to be scanned.

INVESTIGATIVE ANESTHESIA AND MAGNETIC RESONANCE IMAGING

The technology of MRI spectroscopy allows the scientist to study physiologic cellular events as they occur naturally, *in vivo*, rather than in a reconstructed test tube environment. This is because MRI non-invasively monitors the intracellular concentrations and kinetic properties of organic compounds. Investigational techniques have used other organic ions, namely ^{31}P , which is the key ion involved in energy metabolism and oxidative phosphorylation.

In several studies^{1, 6, 17, 20, 25} this new technology was applied to problems of interest to the anesthesiologist. Wyrwicz and associates²⁵ demonstrated that ^{19}F could be used with MRI to study anesthetic uptake and elimination *in vivo*. These studies were controversial because they suggested that anesthetic elimination from the brain was prolonged well beyond the time predicted previously by conventional methods. In other words, the rate of elimination of halothane from rabbit brains was ten times slower than the expected rate, calculated with tissue-blood solubility coefficients and cerebral blood flow. This raised questions about clinically prolonged anesthetic action after short periods of general anesthesia. Later work by Litt and others⁹ used a modified technique in rats and found that halothane was entirely eliminated within 1 hour after a stable 90-minute anesthetic. They concluded that the Wyrwicz study was flawed in that it detected a significantly larger signal, probably resulting from halothane metabolites and extracerebral tissues. A study by Evers and colleagues⁶ also used MRI and fluoride ion to investigate the theories of the molecular mechanism of volatile anesthetics. Their data suggested the existence of a saturable anesthetic site for halothane in the brain, rather than supporting the older theory that halothane causes anesthesia by means of nonspecific membrane perturbations.

Despite differences in methodology and results, the studies mentioned previously have yielded exciting results. MRI allows the investigator to look at analytic biochemical processes in an *in vivo* setting. This major scientific breakthrough should promulgate future research about the mechanism of action of the potent inhalation agents.

SUMMARY

MRI is a diagnostic technique that employs a strong magnetic field and RFs to generate images. The magnetic field provides interesting challenges to members of the anesthesia team: prohibitive use of any ferromagnetic material (which is attracted to the magnet), image degradation from monitoring equipment, and malfunction of routine electronic monitors kept within the vicinity of the scanner. Therefore, major changes are needed regarding the choice of anesthetic and mon-

itoring equipment to ensure the safe delivery of anesthesia. This review highlights these problems and offers some solutions. MRI is also being used as an investigative tool to define the action and kinetics of the potent inhalation anesthetics. It is therefore of critical importance that we learn more about this exciting new frontier in imaging.

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Anesthesia for In Vitro Fertilization

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The concept of in vitro fertilization (IVF) and embryo transfer has interested reproductive physiologists for several decades. Chang⁹ achieved success with extracorporeal fertilization in rabbits. During the following years veterinarians used this technique with cattle, sheep, pigs, and horses.¹⁵ Steptoe and Edwards⁴⁰ originally devised the technique for human IVF for relief of otherwise intractable tubal occlusive problems. They achieved the first two live births in 1978 and 1979, after completing 109 embryo transfers. The Department of Obstetrics and Gynecology at Eastern Virginia Medical School achieved success by 1981 and became the first IVF center in the United States. By 1982, IVF had produced over 100 children worldwide. Presently, this technique has resulted in over 3000 babies. Although only 10 years have passed since the birth of the first human conceived through IVF, this method has emerged as an effective alternative for many infertile couples.¹⁸ Currently, more than 100 American medical centers offer IVF, and many more plan to provide the service in the future. More than 25 established programs exist in Great Britain.

In 1982, the Board of Directors of the American Fertility Society recognized IVF as an acceptable treatment for infertility in couples in which the wife has absent or irreparable damage of the fallopian tubes. The method circumvents the blocked fallopian tubes by harvesting the mature egg, most commonly via laparoscopy, just prior to its discharge from the follicle. Following transfer to an external medium, exposure to sperm takes place, fertilization occurs, and development transpires in a controlled environment. Finally, the fertilized egg is returned to the uterine cavity for continued maturation.¹⁷

In vitro fertilization and embryo transfer represent a labor-intensive undertaking requiring as many as 20 staff members. Successful IVF programs necessitate integration of physicians and technologists with diverse skills and backgrounds: a reproductive endocrinologist to supervise and monitor follicular development, a surgeon skilled in

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laparoscopy, oocyte retrieval, and embryo transfer, and technicians to prepare the required special growth media. Additionally, hospital laboratories must be able to perform daily assays of plasma hormone levels.⁴⁵ During the course of a treatment cycle, the IVF team must function 7 days a week. All of this points to the advantage of associating IVF with a large hospital, especially one affiliated with academic medicine.¹⁷

The surgeon and the patient often incorrectly classify the surgery and anesthesia required for IVF as minor events, because oocyte retrieval requires a small skin incision, can be accomplished quickly, and takes place in an ambulatory surgery facility. However, the ability to perform a safe and successful anesthetic for IVF calls for attention to many important aspects of the procedure. Recovery from anesthesia must occur rapidly with a minimum of side effects. The anesthesiologist should understand and cope with the physiologic implications of pneumoperitoneum, Trendelenburg's position, and the use of intraperitoneal CO₂, while minimizing the associated risks of gastric acid aspiration, gas embolism, hypoxia, hypercarbia, and nerve damage.

OBSTETRIC CONSIDERATIONS

Patient Selection and Evaluation

Initially, only women with damaged or absent fallopian tubes qualified for IVF, but the indications have recently broadened to include male factors, endometriosis, cervical mucus abnormalities, or unexplained long-term infertility. Although artificial insemination with donor sperm proves effective when the husband has oligospermia, a rather common cause of infertility, many couples now reject this alternative and select IVF, which gives them a chance to have their own child.¹⁸ Patients with endometriosis who fail to conceive following surgery and hormone therapy are excellent candidates for IVF. Unexplained infertility may be due to defects in the sperms' fertilizing ability, the oocytes' ability to be fertilized, or the ability of the embryo to implant in the uterus.³²

Pretreatment screening of all couples ensures that no alternative therapy exists and that a reasonable chance of success with IVF can be anticipated.³² During the initial visit, the IVF team carefully reviews the infertility history including past evaluations and medical and surgical treatment. For patients with a history of extensive pelvic surgery and abdominal adhesions, a screening laparoscopy or hysterosalpingogram may be necessary to establish the feasibility and safety of ovum aspiration.¹⁸

Usually, laparoscopy represents a relatively safe, low-risk procedure; however, it should not be performed on patients for whom anesthesia would be contraindicated or patients with chronic medical problems that render pregnancy unsafe.

If diabetes mellitus, thyroid disease, or hypertension exist but do not contraindicate pregnancy, the disorders should be properly controlled during the preconception period. Patient counseling with regard to dietary habits, smoking, and alcohol consumption increases the chances of successful outcome of pregnancy once fertilization and implantation occur.¹⁶ Finally, an andrology survey of the partner is an important area of investigation, to determine the adequacy of motile sperm and to rule out infection.²³

Methodology

The process of IVF involves obtaining mature oocytes and incubating them with sperm. The IVF team transfers the resulting embryos into the uterine cavity where they implant, and, it is hoped, pregnancy progresses naturally.

Timing of Aspiration. An attempt to stimulate multiple ovarian follicles constitutes the initial procedure in IVF. Most programs employ combinations of clomiphene citrate, human chorionic gonadotropin (hCG), follicular-stimulating hormone (FSH; Metrodin), or gonadotropin-releasing hormone (GrRH) to induce oocyte recruitment with the goal of aspirating preovulatory oocytes just before release from the follicle. Oocyte collection takes place as close as possible to the time of expected ovulation to avoid immature oocytes if done too early or spontaneous ovulation if done too late.¹¹ Daily cervical mucus analysis and serum estrogen levels help determine the best time for oocyte aspiration. Ideally, ultrasound examination will reveal a minimum of two follicles more than 15 mm in diameter just prior to aspiration.

Aspiration Procedures. The gynecologist usually aspirates the follicles early in the morning to prevent emergencies from delaying the procedure. He or she must obtain a large number of oocytes because the pregnancy rate improves as the number of embryos transferred to the uterus increases. DeCherney and Lavy¹¹ recommend aspiration of follicles measuring more than 10 mm; smaller follicles tend to contain immature oocytes that have a lower fertilization rate.

Follicle aspiration may be achieved by laparoscopy or by ultrasonographically guided aspiration via the vagina. With the transvaginal technique the gynecologist aspirates ovum by passing an ultrasound probe through the fornix (Fig. 1). In comparison, direct visualization of the ovaries represents the major advantage of the laparoscopic technique; however, laparoscopy usually requires general anesthesia with its associated side effects. Furthermore, the presence of adhesions occasionally renders the ovaries inaccessible, decreasing the success of the procedure. Although laparoscopy serves as the traditional and most widely employed method, over the past few years the ultrasonographically guided technique has emerged as a viable alternative. Aspiration can be performed from either freely mobile ovaries or those bound by adhesions. The ultrasound method harvests fewer oocytes than laparoscopy; however, both methods produce a similar number of successful pregnancies.³ In comparison to laparos-

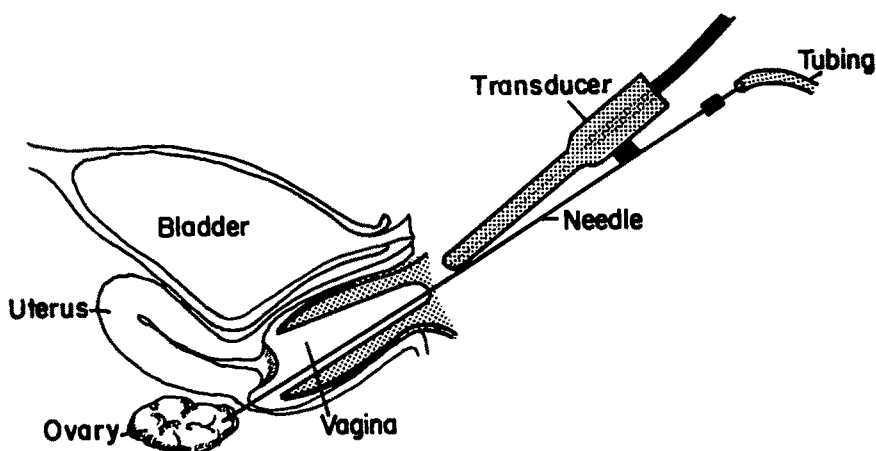


Figure 1. Locating and aspirating the follicle. The vaginal sector transducer is used for transvaginal ultrasound-guided follicular puncture. Once the puncturing plane has been located, the needle is inserted into the follicle.

copy, ultrasound technique offers the potential benefits of less trauma, less morbidity, decreased operating room and personnel time, and greater patient acceptance as well as decreased expense (Table 1). The transvaginal transducer allows for superior imaging of the follicles due to its proximity to the ovaries. A needle guide can be attached to a groove in the transducer scanner, which permits the introduction of the ovum aspirating needle in the field of view (see Fig. 1).

Semen Preparation. The partner donates semen 2 to 4 hours before insemination after abstaining from sex for 3 to 5 days. Technicians liquefy the semen, mix it with insemination medium, and incubate it for about 30 minutes in an atmosphere of 5 per cent CO_2 . They then inseminate the oocyte with a solution containing 1 million sperm in 3 mL of insemination medium.¹

Fertilization, Cleavage, and Embryo Transfer. Once obtained, follicular contents are examined in a laboratory adjacent to the operating room. Following identification and isolation from the fluid, the oocyte is placed in a culture dish containing the sperm, insemination medium, and fetal serum. Transfer to the uterus occurs most

Table 1. *Advantages of Transvaginal Ultrasound Technique for Aspiration of Oocytes*

Avoids general or regional anesthesia
Avoids the risk of laparoscopy, pneumoperitoneum, Trendelenburg position
Less postoperative morbidity as compared with laparoscopy
Greater patient acceptance than laparoscopy
Aspiration can be performed on ovaries with adhesions
Excellent imaging of follicles with ultrasound

commonly when the embryo reaches the four- to eight-cell stage. An early transfer offers the theoretical advantages of shortening the time the embryo remains in an artificial medium and hastening the time of return to a natural environment. Later transfer, however, allows for more precise control and monitoring of the embryo's development. Transfer usually takes place 40 to 50 hours after insemination.¹

Once normal embryo development is confirmed, the patient moves to a room close to the surgical suite and is positioned appropriately for embryo transfer. An anterior uterus calls for a knee-chest position, whereas a posterior uterus indicates the dorsal lithotomy position in order to keep the fundus lower than the cervix. The embryos are placed in a transfer catheter and introduced into the uterine cavity. After transfer, the patient remains in the prone or supine position for 4 hours and then stays relatively inactive for an additional 48 hours.¹⁸ Embryo transfer requires minimal medication; a small intravenous or oral dose of diazepam or midazolam suffices for particularly anxious patients. Commencing with the day of embryo transfer, many IVF centers dispense progesterone (suppositories or injections) to ensure adequate endometrial development.

Gamete Intrafallopian Transfer Procedure. When at least one fallopian tube is patent, the gynecologist can employ an alternative to IVF: gamete intrafallopian transfer (GIFT).⁶ This procedure, first performed in 1984, involves placing a couple's gametes, ova and sperm directly into the fimbriated end of the fallopian tube via laparoscopy. Usually no more than two oocytes are introduced into each fallopian tube. The GIFT technique appears to be a more physiologic approach than IVF, because the ampullary region of the fallopian tube is the site of fertilization in the human, and the embryos are able to develop to a more mature stage before moving to the uterus. The procedure is contraindicated in patients with damaged tubes in whom the risk of ectopic pregnancy is high. The GIFT process does not require in vitro culture techniques and embryo transfer can mean a savings of several thousand dollars as compared with IVF.

Outcome of In Vitro Fertilization

In the early years of IVF (1978 to 1981) the pregnancy rate ranged from 1 to 8 per cent, but a steady rise in successful outcome has followed with the rate currently standing at 15 to 20 per cent. Improved success results from (1) more precise monitoring of the ovulatory process leading to the harvest of a large number of mature oocytes; (2) hormonal stimulation of follicles with improved oocyte recovery; and (3) multiple embryo transfers.²⁹ For example, if the uterus receives one embryo the chance of a pregnancy is about 10 per cent; two embryos increase pregnancy rates to 15 per cent, three embryos to 20 per cent, and four to more than 25 per cent.³⁴ Women 40 years or older experience lower pregnancy rates, that is, less than 10 per cent. Success increases to 12 per cent in women between 30 to 39 years of age and is highest in those under 30 years. Difficulty in stimulating ovulation may partially account for the lower success rates in older

women; however, the reduced quality of ova and endometrium may also play a significant role.²⁵

The extraordinary nature of conception in pregnancies achieved with IVF increases the possibility of fetal abnormalities such as multiple gestation, abortions, ectopic pregnancy, and chromosomal abnormalities. Several factors contribute to this increased obstetric risk: (1) these women tend to be older, often having a history of previous reproductive losses or endocrine problems, and (2) they frequently have undergone tubal surgery.⁴²

After pregnancy is well established, obstetric care does not require specific precautions. The decision to routinely perform amniocentesis remains controversial. Two cases of spontaneous abortion have already been reported following complications of amniocentesis in IVF patients. Most centers perform this test only for usual indications, such as advanced maternal age, history of neural tube defects, or certain sex-linked carrier states.²⁴ Ultrasonographic studies qualify as less controversial; although no evidence suggests that a viable pregnancy calls for an ultrasound examination, given the benign nature of the test and the newness of the IVF process, most centers use this screening technique.¹⁶

Multiple Gestation. Multiple gestation occurs ten times more often following IVF than in natural cycles. The practice of transferring many embryos causes this high incidence.²⁴ Multiple gestation predisposes to an increased rate of prematurity, pregnancy-induced hypertension, and fetal loss. Multiple pregnancy presents a real concern and may have a rate as high as 25 to 35 per cent. Overall, multiple gestation rates stand at 10 per cent for twins, 1.4 per cent for triplets, and 0.3 per cent for quadruplets. The risk of multiple conceptions limits the number of embryos transferred. Most IVF programs transfer a maximum of three to four embryos, which give an excellent chance of success and limits the multiple pregnancy rate to 15 to 25 per cent.²⁵

Ectopic Pregnancy. Ectopic pregnancy following IVF occurs three times more often than in the normal population. Retrograde transport of the embryo, excessive volume of transfer medium, a forceful injection close to or into the tubal ostia, pre-existing tubal disease, and previous tubal surgery account for the increased rate.

Congenital Malformations. An increased possibility of congenital malformations represents a major concern following IVF. Factors influencing the development of chromosomal abnormalities and congenital malformations include advanced age, maternal drugs used to stimulate ovulation, and the procedures used to prepare the sperm and oocyte, including mechanical manipulation, artificial growth media, exposure to light, and fluctuating temperatures. Based on the limited data available, no evidence of an increase in the incidence of congenital malformations after IVF exists; final conclusions await larger numbers of conceptions.^{24, 25}

Spontaneous Abortion. Inclusion of those cases in which maternal blood levels of B-hCG increase initially and then decline pushes the incidence of spontaneous abortion after IVF to 50 to 80

per cent. Most of these "abortions" represent "failed chemical pregnancies," indicating early problems with implantation rather than early abortion after successful implantation.⁴² In contrast, spontaneous abortion after the absence of one menstrual period occurs in 12 to 30 per cent of IVF pregnancies. The likely causes of abortion include chromosomal abnormalities of the embryo, inadequate function of the corpus luteum, and inadequate development of the endometrium. Remember, however, that approximately 15 per cent of normal conceptions result in spontaneous abortions.

Cesarean Section. No evidence suggests that a favorable outcome requires a cesarean section providing that the pregnancy has been uncomplicated.¹⁶ However, IVF pregnancies appear to be associated with a high cesarean section rate (33 to 56 per cent)^{5, 24} most likely resulting from increased numbers of multiple gestations, older maternal age, and a high incidence of pregnancy-induced hypertension. The later problem most likely reflects the advanced age, multiple gestation, and the primigravidity of the typical IVF patient. The obstetrician's concern for the "premium nature" of these pregnancies also contributes to the unusually high incidence of cesarean section.⁴⁷

It is vital to follow up the progress of children conceived by IVF in order to detect any adverse outcomes in their physical and psychological development; there should also be some assessment of the parent-child relationship. Only careful study of thousands of IVF pregnancies and the children will provide definite conclusions about the fetal and maternal risks of the procedure.

Legal and Ethical Aspects

Some members of the legal profession as well as the lay public view IVF as an unwarranted method that tampers with the "sacred" issue of creation. Physicians involved in IVF need to be especially sensitive to these legal and ethical considerations.¹⁴ The Constitution of the United States protects people's procreation decisions. The United States Supreme Court stated that individuals have a right to be free from government control regarding their decision of whether or not to bear a child. However, no federal money has been awarded for human IVF research.

In many respects, the law has failed to keep pace with the rapid advances made in reproductive technology. In vitro fertilization propagates more sophisticated legal issues than present laws can address.⁴ Because many types of infertility treatments are new, there is little legal precedence to guide physicians regarding the legal standards required in IVF.¹⁹ Some states have adopted specific IVF laws. For example, Pennsylvania requires that anyone conducting IVF must file quarterly reports with the Department of Health. These reports include the names of personnel assisting in the process, the location and names of the sponsoring institution, the number of eggs fertilized, the number of embryos destroyed, and the number of women implanted with embryos.

Litigation in the area of IVF usually relates to the physician's

Table 2. *Complications of Laparoscopy and Pneumoperitoneum*

Accidental insufflation of the abdominal wall, retroperitoneum, mesentery, omentum, and bowel
Hypercarbia from excessive absorption of carbon dioxide
Ulnar nerve injury
Decreased lung volumes due to Trendelenburg position and pneumoperitoneum
Gas embolism
Pneumothorax
Hemorrhage from Veress needle or trocar

negligence in handling fertilized ova or embryos, difficulties in performing the oocyte retrieval or transfer, and failure to obtain informed consent. Proper informed consent must include information on the process of IVF, including its dangers, a realistic estimate of the success rate of IVF at that particular center, and alternatives to IVF that also allow conception. Finally, the physician should discuss with the patient the protocol for disposal or preservation of ova that are fertilized but not implanted.^{4, 19} The most controversial issue is the status of the embryo. IVF embryos could provide valuable information that might lead to advances in infertility treatment and in contraception development. They could also be used to test the effects of medicine or suspected toxins.³³ The Ethics Advisory Board of the Department of Health and Human Services states that the human embryo is entitled to respect, but not the full legal and moral rights attributed to persons, and that research on embryos is not to be carried out in the laboratory beyond implantation stages.

All IVF teams should have the aspects of their program approved by the institution's research committee. Once established, members of the teams should report periodically to the research committee concerning all medical aspects of the treatment cycle, including a record of successes and failures with respect to oocyte retrieval, fertilization, transfer, subsequent pregnancies, and complications.²²

ANESTHETIC CONSIDERATIONS

Risks of Laparoscopy

Despite the low mortality and morbidity associated with laparoscopy, the occasional occurrence of a catastrophic complication demonstrates that follicular aspiration carries some risk (Table 2). Aspiration of follicles via laparoscopy requires the creation of the pneumoperitoneum, which can result in a significant number of complications. The lower margin of the umbilicus represents the ideal site for the insertion of the Veress needle, followed by the trocar, sleeve, and laparoscope. This relatively avascular area is the thinnest portion of the abdominal wall; adhesions rarely occur here.⁸ An incorrectly

placed needle may insufflate the abdominal wall, retroperitoneum, mesentery, omentum, or bowel.

Pneumoperitoneum. CO₂ and nitrous oxide are used for producing the pneumoperitoneum. High solubility, which permits rapid absorption of any gas remaining postoperatively and a margin of safety if accidentally injected intravascularly, makes CO₂ the gas of choice. The theoretical possibility of altering the pH of the follicular fluid presents the main concern with the use of carbon dioxide. The transperitoneal pressure gradient into the blood may produce hypercarbia. Nitrous oxide is not absorbed during pneumoperitoneum in quantities sufficient to cause hypoxia nor does it sustain combustion.¹⁰ Nitrous oxide proves especially helpful when performing the operation with local analgesia because it causes less diaphragmatic and peritoneal irritation than carbon dioxide.³⁶

Trendelenburg Position. Laparoscopy requires the Trendelenburg position, which displaces abdominal organs to gravitate toward the diaphragm and out of the pelvis, making the ovaries easily visualized and assessable. Meticulous care and proper positioning reduces the severity of soft-tissue and neurologic complications associated with this operative requirement. One of the patient's arms should be at her side so that the surgeon can be in the optimum position to operate. The superficial course of the ulnar nerve mandates adequate padding of the elbow. Shoulder rests can be used to prevent the patient from sliding off the operating table when tilted greater than 45 degrees. However, the braces can produce brachial plexus injury, the most common neural complication of Trendelenburg position, by depressing the clavicle into the retroclavicular space, causing direct compression and stretching of the nerve roots. Prevention depends on careful positioning of the arms at the patient's side, or if extended, the arm must not be hyperextended. One should caution the surgeon about leaning on the patient's extended arm and place the shoulder rest at the acromioclavicular junction, and not over the clavicle.³⁷

Cardiac Complications. Laparoscopy alters cardiac physiology. Severe hypotension and cardiac arrest rarely occur, but less significant changes, such as mild decrease in arterial pressure and cardiac output, happen commonly. These cardiovascular changes result from the head-down position and pneumoperitoneum.⁷ When intra-abdominal pressure exceeds 30 mm Hg, venous return diminishes and produces significant decrease in central venous, arterial, and pulse pressures and a small decrease in cardiac output.³⁰ The pneumoperitoneum sequesters blood in the legs and reduces the circulating blood volume. Routine intraoperative blood pressure and heart rate monitoring may not indicate a drop in cardiac output because compensatory reflex mechanisms usually operate effectively in healthy woman.⁷ At the conclusion of the operation the patient should be slowly returned to the horizontal position, allowing for a gradual displacement of blood from the thorax and upper extremities into the lower extremities. This will decrease the incidence and severity of hypotension.³⁷

Pulmonary Complications. Together, the Trendelenburg posi-

tion and the pneumoperitoneum produce cephalad pressure on the diaphragm and significantly reduce vital capacity. Restriction of lung capacity and increased pulmonary blood volume result from the head-down tilt. These factors decrease pulmonary compliance, diminish functional residual capacity, and compromise aeration of the lower lobes, all of which may cause postoperative atelectasis.⁷

Alexander et al² reported a significant rise in PaCO₂ and a fall in pH in patients undergoing laparoscopy with general anesthesia when CO₂ produced the pneumoperitoneum. Increased absorption of CO₂ from the peritoneal cavity caused the hypercarbia. The blood rapidly absorbs CO₂ because of the high difference in partial pressures between the pneumoperitoneum and blood perfusing the abdomen. During laparoscopy, spontaneous ventilation can be associated with significant hypercarbia because of diminished alveolar ventilation coupled with exogenous CO₂ absorption. Controlled ventilation and the use of a respirometer and especially an end-tidal gas analyzer obviates this problem.

Steep Trendelenburg position requires endotracheal intubation. The position of the endotracheal tube should be confirmed after the Trendelenburg position is assumed because the mediastinum may shift in a cephalad direction causing the endotracheal tube to pass into a bronchus.³⁶

Gas embolism rarely occurs but represents a potentially fatal complication of laparoscopy. Intravascular injection of gas may follow direct needle or trocar placement into a vessel or develop indirectly from insufflation of gas into an abdominal organ. A high index of suspicion when cardiac arrhythmias and hypotension occur aids early diagnosis. The characteristic auscultatory changes in heart sounds occur later (mill wheel murmur). Precordial Doppler ultrasound provides the most sensitive method for detecting a gas embolism. End-tidal gas analysis also proves helpful.⁷

Pneumothorax forms another potentially serious complication. Gas may dissect retroperitoneally, through congenital foramina and produce a pneumomediastinum. Alternatively, it may enter the chest cavity through defects in the diaphragm or via weak points of the aortic and esophageal hiatus. Cyanosis or hypotension, subcutaneous emphysema, or an increase in peak inspiratory pressure constitute signs of pneumothorax. When awake, patients may complain of dyspnea and chest pain. Hyper-resonance on chest percussion and absent or diminished breath sounds provide further evidence for pneumothorax.¹²

Hemorrhage. Hemorrhage from laparoscopy accounts for almost half of all complications. Blood vessel injuries range from minor bleeding from superficial vessels to massive hemorrhage due to lacerations of major retroperitoneal vessels. Both the Veress needle and the trocar can produce vascular trauma.⁷ Blind insertion of the needle and trocar demands strict attention to anatomic landmarks and safe insertion techniques, including the use of sharpened instruments, adequately established pneumoperitoneum, elevation of the abdominal wall,

avoidance of lateral needle and trocar insertion, and Trendelenburg position.

Anesthetic Management

Premedication. Oocyte retrievals are usually outpatient procedures; therefore, the anesthesiologist and anesthetist must ensure that the patient will recover quickly and be able to safely leave the medical center within a few hours after the procedure. With these goals in mind, most clinicians avoid premedication with sedatives or long-acting narcotics. The preanesthetic visit may alleviate anxiety more effectively than use of drugs. Providing the patient with a pleasant waiting area and permitting continued support from a relative or friend until the time of surgery will help the patient remain calm.²⁶

Ong et al³¹ demonstrated that nonobese adult outpatients undergoing elective surgery face a greater risk of aspiration pneumonia than in-patients because of large volumes of highly acidic gastric contents. In a study by Manchikanti and colleagues,²⁸ 88 per cent of unpremedicated patients had a gastric pH less than 2.5, and 56 per cent had gastric volumes greater than 25 mL with a pH less than 2.5. They also observed that premedication with either diazepam, hydroxyzine, or prochlorperazine did not alter the pH or volume of gastric juice as compared with patients given no premedication. These findings prompt anesthesiologists to consider the administration of histamine-2 receptor antagonists and gastroprokinetic drugs, such as metoclopramide to all patients undergoing IVF. Nevertheless, no convincing evidence demonstrates that prophylactic therapy eliminates pulmonary damage or reduces mortality following aspiration.

In recent years, anesthesiologists have successfully employed local, regional, and general anesthesia for laparoscopy. The ideal anesthetic for follicular aspiration would avoid oocyte toxicity, minimize the stress of laparoscopy, permit rapid recovery, be devoid of effects following repeated administration, and cause minimal side effects.¹

Local Anesthesia. Local anesthesia offers the advantages of reduced anesthesia time, faster recovery, less nausea and vomiting, fewer postoperative complications, and lower cost of administration when compared with other anesthetic techniques.^{38, 39} The patient who is awake facilitates early diagnosis of complications such as CO₂ embolization, pneumothorax, and hemorrhage. Finally, the surgeon can demonstrate anatomy and pathology directly to the patient by means of a fiberoptic teaching extension. Local anesthesia for follicular aspiration, although technically easy, proves unsuitable for most patients. Unlike laparoscopy for tubal ligation, follicular aspiration requires multiple puncture sites and considerable abdominal and pelvic organ manipulation. The need for steep Trendelenburg position and for a necessarily large pneumoperitoneum make breathing difficult. The severe head-down tilt causes intracranial blood stasis resulting in significant discomfort. Therefore, the patient undergoing laparoscopic oocyte retrieval with local anesthesia must be cooperative, calm, and able to withstand mild to moderate pain.

For the transvaginal approach for follicular aspiration, the vaginal wall is anesthetized. The anesthesiologist administers small incremental doses of short-acting narcotics and sedatives as required for patient comfort. Numerous drugs and drug combinations have served to supplement local anesthesia. Unanimity of opinion regarding superiority of one type of drug therapy has not evolved. However, this author prefers a combination of intravenous fentanyl and midazolam. The administration of the drugs in appropriate doses with proper patient monitoring is most important. That is to say, intravenous sedation requires trained personnel to monitor the patient's airway, ventilation, and other vital functions because narcotics and most sedatives can substantially depress respiration.

Regional Anesthesia. Regional anesthesia, frequently used for laparoscopic tubal ligation and diagnostic laparoscopy, is less frequently employed for oocyte retrieval. Spinal and epidural blocks offer the advantages of decreasing narcotic and sedative requirement and produce excellent muscle relaxation. Regional anesthesia also avoids the postoperative discomforts associated with general anesthesia, such as sore throat, nausea, myalgias, and airway trauma. Recovery time is relatively fast following use of lidocaine or 2-chloroprocaine. However, surgical manipulation, steep Trendelenburg position, and pneumoperitoneum can impair spontaneous ventilation. Some anesthesiologists avoid spinal anesthesia in young women for fear of postlumbar puncture headaches, whereas other centers do not administer epidural anesthesia because the block takes a relatively long time to administer and "set-up."

General Anesthesia. In spite of the recent popularity of local and regional anesthesia, the vast majority of laparoscopic follicular aspirations are performed using general anesthesia. The method provides excellent muscle relaxation, the ability to control ventilation, elimination of patient anxiety, complete analgesia and amnesia, and a quiescent operative field. No ideal technique or superior combination of drugs exists for general anesthesia for follicular aspiration. Regardless of the method chosen, patient safety, comfort, and rapid discharge from the outpatient center should be its goals. Additionally, the selected approach should minimize nausea, headache, sore throat, and muscle pains.²⁶

Following an intravenous induction with thiopental we commonly maintain anesthesia with 65 per cent nitrous oxide and oxygen and low concentrations of isoflurane. We also administer short-acting narcotics and muscle relaxants. The use of steep Trendelenburg position, high intra-abdominal filling pressure, low pH, and large volumes of gastric contents mandate tracheal intubation.

Induction with a short-acting barbiturate is employed for most outpatient general anesthesiologists. Endler¹³ has demonstrated thiamylol in the follicular fluid as early as 13 minutes after intravenous injection. Nitrous oxide also proves to be particularly useful in the outpatient setting by decreasing the requirement for longer-acting agents.²⁶ Prolonged nitrous oxide exposure can interfere with DNA synthesis and

can theoretically produce a detrimental effect on early embryonic development. Because nitrous oxide inhibits methionine synthesis activity, Roizen and coworkers³⁵ investigated its effects on oocyte function. On the basis of their findings, they concluded that nitrous oxide does not decrease success rates of IVF nor increase the frequency of chromosomal abnormalities. This author does use nitrous oxide and feels that it is not toxic to the developing fetus.

Successful pregnancies have followed the use of oocytes obtained after prolonged general anesthesia. However, the harvesting team should prepare the abdomen and all necessary equipment prior to the induction of anesthesia to minimize exposure time because prolonged exposure to anesthetics may adversely affect oocyte survival.¹¹ A study by Hayes and coworkers²⁰ reveals a negative effect of prolonged exposure to anesthetics and CO₂ pneumoperitoneum on human oocytes in vitro. In this study, anesthesia was induced with thiopental or thiamylal and was maintained by the use of fentanyl and nitrous oxide/oxygen, isoflurane/oxygen, or a combination of these agents. Succinylcholine was employed for muscle relaxation. Oocytes retrieved after prolonged anesthesia time cleaved less frequently as compared with eggs aspirated shortly after induction. Therefore, I recommend minimum exposure of the oocytes to anesthetic agents and CO₂ pneumoperitoneum.

Intubation and surgery requires muscle relaxation. The use of an intermediate-duration, nondepolarizing relaxant such as vecuronium or atracurium for both intubation and surgery will avoid the use of succinylcholine, thereby eliminating myalgias. Outpatients experience a significantly greater incidence and severity of the muscle pains than in-patients.

To maintain general anesthesia, the use of a small amount of a potent inhalation agent ensures amnesia. Isoflurane has the lowest blood/gas coefficient (1.3) and the shortest elimination time. It also undergoes the least metabolism, reducing patient as well as oocyte exposure to metabolites that might have the potential for delayed toxicity.⁴¹ In comparing halothane, enflurane, and isoflurane for a short anesthetic, no single agent appears to be superior to others in facilitating quick discharge from the recovery room.⁴³

Intraoperative narcotics reduce the necessary concentration of potent inhalation agent while minimizing pain at the end of surgery. The narcotic employed must have a rapid onset, short duration of action, and produce minimal cardiovascular effects. Fentanyl has these favorable characteristics. Following intravenous injection, analgesia occurs within 2 minutes and lasts about 45 minutes. Doses of 1 to 2 µg per kg usually suffice for general anesthetics on outpatients.²⁶ The use of narcotics does not appear to have a negative effect on IVF.

Postoperative Pain. Following laparoscopy, all patients experience some discomfort. Incisional pain, diffuse abdominal discomfort, and referred shoulder pain are the most common symptoms. If succinylcholine was used, generalized myalgia commonly develops. In most patients, incisional and abdominal discomfort is usually mild.

Moderate to severe pain can result from a subcutaneous or subfascial hematoma necessitating appropriate examination by the gynecologist.³⁴ Irritation of the subdiaphragmatic peritoneum causes referred shoulder pain because diaphragmatic sensory innervation travels with phrenic nerve. Although having disadvantages for laparoscopic oocyte retrieval, regional anesthesia reduces the incidence of postoperative pain and facilitates its control. Most patients are managed with general anesthesia and, in those expected to have a low pain threshold, incisional pain is prevented by local anesthetic infiltration of the wound. When required, small doses of analgesics given intravenously provide the safest and most efficacious method of pain control in the recovery room. Fentanyl, 25 to 100 µg, usually brings rapid relief of discomfort without delaying discharge.

Postoperative Nausea and Vomiting. Nausea and vomiting commonly follow general anesthesia and can be severe enough to require hospitalization, particularly after laparoscopy, which causes diaphragmatic irritation and nausea. A host of antiemetics have been used in an attempt to control this disturbing side effect. Intraoperative administration of droperidol, 0.625 to 1.25 mg intravenously, appears to prevent postoperative nausea without producing significant sedation.⁴⁴ Nitrous oxide increases middle ear pressure and distends the gastrointestinal tract and thereby may increase the incidence of nausea and vomiting. Lonie and Harper²⁷ studied the effects of nitrous oxide on postoperative vomiting in women undergoing laparoscopy. They observed that patients receiving nitrous oxide had a significantly higher incidence of vomiting than women who did not receive the anesthetic. Other studies have not supported the contention that nitrous oxide contributes to nausea and vomiting. In fact, this author does administer nitrous oxide to outpatients.

FUTURE OF IN VITRO FERTILIZATION

Since the first IVF baby was delivered, many changes and improvements have taken place. Although the pregnancy rate for IVF now approaches 25 per cent, many technical and theoretical problems remain to be solved. Among these are determining the best method for stimulating multiple follicles and improving the techniques to ensure retrieval of the most mature oocytes. Better media and culture environment could improve embryo growth in vitro. Also of importance is the need to reduce embryo trauma during transfer to the uterus.^{22, 29}

Extra embryos can be frozen and subsequently thawed and transferred, although only about half of the embryos presently survive freezing and thawing.²² Cryopreservation of human embryos, therefore, requires further study. Screening of embryos for genetic disease constitutes an area of intense investigation. Workers are developing DNA probes to detect genetic abnormalities. IVF could be offered to

couples at risk for genetic disease. Two or more cells could be removed from the embryo and tested for an abnormal or absent gene.²²

Despite the necessary time commitment, the operative risks involved, and the costs of up to \$6000 per cycle (plus \$2500 for screening), many previously infertile couples are deciding that IVF offers a reasonable chance of pregnancy.

SUMMARY

This article presents the important aspects of IVF including its history, indications, technical aspects, and outcome. Oocyte retrieval requires the presence of an anesthesiologist. For laparoscopic aspiration of oocytes, general anesthesia reduces patient anxiety and provides excellent muscle relaxation, good operative conditions, and better control of ventilation. The use of general anesthesia mandates endotracheal intubation. Although no specific general anesthetic regimen is preferred, oxygen, nitrous oxide, and small doses of potent inhalation agents and short-acting narcotics provide intraoperative analgesia and amnesia, and minimize postoperative discomfort. Knowledge of the physiologic changes that occur with Trendelenburg position and pneumoperitoneum, and vigilance for signs of hemorrhage and gas embolism are essential in avoiding serious complications. At present, no anesthetic agent or combination of drugs has been shown to be more or less toxic to human oocytes. However, few comparative studies have addressed this subject; certainly, good studies are needed.

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